FDA Advisory Committee Briefing Document

Peripheral and Central Nervous System Drugs Advisory Committee

Meeting to be held on January 20, 2011

New Drug Application 202-008
Amyvid™ (Florbetapir F 18 Injection), sponsored by
Avid Radiopharmaceuticals

This document was prepared on December 20, 2010

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This document contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains preliminary assessments and/or conclusions and recommendations written by individual reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. Discussions by the committee as well as subsequent data submissions by the applicant may change all draft/preliminary review observations. We have brought this issue to this advisory committee in order to gain the committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion at the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

1. Introduction

Amyvid (Florbetapir F 18 Injection) is a drug proposed for marketing with the following indication:

"Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain."

The applicant proposes intravenous injection of 10 mCi of the drug followed 30 to 50 minutes later by a 10 minute image acquisition period. Following image reconstruction, the image interpreter evaluates the brain images to make a binary assessment of amyloid plaque presence (positive or negative).

The FDA brings this NDA to the Advisory Committee to obtain the committee's perspectives on the strengths and limitations of the major clinical and nonclinical data and to assess these data in the context of the drug's proposed clinical use. The FDA review team makes the following preliminary observations:

The nonclinical and clinical database:

- Appears to support the contention that Amyvid images detect brain amyloid plaque, based upon the use of a negative/positive threshold level (proposed to correspond to a modified CERAD plaque histopathological score of "more than sparse" neuritic plaques).

- Was designed to assess the extent of amyloid plaque within the brain. The clinical development program was not designed to demonstrate the usefulness/utility of the information obtained from brain amyloid imaging. A 2008 FDA advisory committee noted that brain amyloid imaging "could" have clinical utility and that imaging drug development programs intended to assess amyloid content of the brain should use histopathology as a standard of truth (see minutes).

- Safety aspects appear consistent with that for approved diagnostic radiopharmaceuticals. To date, no troublesome safety signals have been detected, based upon an exposure of approximately 500 subjects.

Within the single phase 3 clinical trial:

- Reader training consisted of a half-day session that involved a power point presentation of illustrative cases, a practice session with 5 training cases with provided answers, a practice session with 20 training cases with immediate case by case feedback, an optional review of 12 additional training cases (with delayed feedback), a reader test of 25 cases unassisted under simulated study conditions and a review of test results with each reader.

- Images were interpreted by a group of three readers and the group's collective outcome was used in the main efficacy analyses.

- Clinical data were not used in image interpretation.

- Two cohorts of subjects were studied, each with a unique Amyvid image interpretation method:

    - An autopsy cohort: semiquantitative image assessment using a five point scale that is not proposed for use in clinical practice;

    - A cohort of young subjects who presumptively lacked brain amyloid: the "global" image assessment proposed for use in clinical practice.

- Primary endpoints achieved statistical success and were supported by the secondary endpoint results. Specifically, semi-quantitative Amyvid image visual scores correlated with quantitative histopathological content of amyloid plaque; the global image assessments within the cohort of young subjects were all negative.

- The global image assessment method to be used in clinical practice was not used within the full cohort of subjects with the histopathology standard of truth to estimate:

    - Amyvid performance characteristics

    - The extent of variation in reader-to-reader image interpretation results.

In clinical practice:

- Images are to be interpreted as either positive or negative for amyloid plaque using a global assessment by a single reader.

- Will rely upon a reader's skill in determining whether or not the isotope distribution throughout the brain is consistent with the pattern and features used to characterize a positive/negative image in illustrative cases.

- Are to be interpreted without clinical data, unlike many (if not most) clinical image interpretations. The impact of clinical information (e.g., extent of cognitive impairment) upon Amyvid image reliability is unknown.

Overall, FDA's major concerns with the Amyvid application relate to an apparent insufficient development of the reader training methods proposed for clinical use, including verification that these methods ensure acceptable reader-to-reader consistency in image interpretation across a patient population representative of that proposed for clinical use as well as reliability of the image interpretations with respect to the truth standards used in the phase 3 clinical trial.

2. Topics for Questions and Discussion

FDA anticipates questions and discussions related to the following topics:

1. In 2008, an FDA advisory committee noted that the detection of amyloid plaque within the brain could have clinical utility. Conceivably, new scientific and clinical developments since 2008 may have changed this perspective. At the present time, would knowledge of brain amyloid plaque content have clinically usefulness?

2. Do the nonclinical and clinical data establish Amyvid's ability to detect brain amyloid plaque?

3. Discuss the following considerations important to the potential approval of Amyvid:

    a) Do you concur with the applicant's proposal that, "A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain"?

    b) The training methods for clinical readers:

        - How important do you regard these methods? For example, should the use of Amyvid be restricted to clinicians who have completed a requisite training program?

        - Should the sufficiency of the clinical reader training program be verified by premarket testing?

        - Discuss the potential usefulness of reinterpretation of database images by readers who have been trained using the training methods proposed for clinical use.

    c) Labeling that indicates the limitations of Amyvid use, such as avoidance of perceptions that the test may be used to diagnose Alzheimer's Disease or to monitor a patient's clinical status.

3. Diagnostic Drug Efficacy Considerations:

The Amyvid development program was importantly impacted by the regulatory expectations (regulations/guidance) unique to diagnostic radiopharmaceuticals as well as a 2008 FDA Advisory Committee that specifically discussed amyloid imaging detection programs.

Regulations (21 CFR 315) state that FDA's determination of the safety and effectiveness of a Diagnostic radiopharmaceutical includes consideration of:

a) the proposed use of the diagnostic radiopharmaceutical in the practice of medicine

b) the pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical), and

c) the estimated absorbed radiation dose.

The efficacy considerations for imaging drugs (including a diagnostic radiopharmaceutical) are different from those for therapeutic products. Regulations and FDA guidance provide examples of various categories of diagnostic imaging drug efficacy claims (such as anatomical delineation or organ functional assessment) and emphasize that these claims must have clinical usefulness.

In some situations, the clinical usefulness of an imaging drug is self-evident, implicit or already established (e.g., normal and/or abnormal anatomical delineations/broken bone, cerebral hematoma, etc.) such that a clinical development program does not need to re-establish the clinical usefulness of the imaging information. This determination relies upon a thorough understanding of the imaging information, its proposed clinical use and the underlying clinical/medical science. If the clinical usefulness of an imaging drug's information is not self-evident or already established, then the drug's clinical usefulness needs to be established within the drug's development program. Whether or not brain amyloid imaging provided clinically useful information was one of the major discussion topics at the 2008 FDA advisory committee (see attachment).

The regulatory expectations for diagnostic imaging drugs are similar to those expected for other drugs used as diagnostics. To illustrate the range of potential label claims for diagnostic drugs (e.g., disease-specific to physiologic or non-specific), listed below are indication statements for certain approved drugs:

- Fludeoxyglucose F18 Injection; "assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer" (plus other indications);"

- Iobenguane I 123: "indicated for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests;"

- Cosyntropin Injection: "intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency;"

- Methacholine Chloride for inhalation: "indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma."

- Gadoxetate disodium: “for intravenous use in T-1 weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected liver disease.”

These examples illustrate the relatively broad range of potential indications for diagnostic drugs, based upon the database supporting the drug’s approval as well as the proposed clinical use.

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
October 23, 2008

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on October 23, 2008. A verbatim transcript will be available in approximately six weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder08.html#PeripheralCentralNervousSystem

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 23, 2008 at the Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA. The meeting was called to order by Larry B. Goldstein, M.D. (Acting Chair); the conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., BCPS (Designated Federal Official). There were approximately 200 people in attendance. There were three Open Public Hearing (OPH) speakers.

Issue: On October 23, 2008, the committee discussed the clinical development of radionuclide imaging products for the detection of amyloid to assist in the diagnosis of Alzheimer's Disease.

Attendance:
Peripheral and Central Nervous System Drugs Advisory Committee members present (voting): Larry B. Goldstein, M.D. (Acting Chair); Britt Anderson, M.D., Ph.D.; Mark W. Green, M.D., Ph.D.; Gregory L. Holmes, M.D., Ph.D.; Lily K.F. Jung, M.D., M.M.M.; Ying Lu, Ph.D.; Matthew Rizzo, M.D.; Stacy A. Rudnicki, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee members absent (voting): Sandra F. Olson, M.D.

Temporary Voting Members: Twyla Bridgwater (Patient Representative); William E. Bridgwater (Patient Representative); Peter Herscovitch, M.D.; Elizabeth C. Jones, M.D., M.P.H.; Robert F. Mattrey, M.D.; Henry D. Royal, M.D.; Harvey A. Zeissman, M.D.

Industry Representative present (non-voting): Roy E. Twyman, M.D.

Guest Speakers (non-voting): Madhav Thambisetty, M.D., Ph.D.; G. William Rebeck, Ph.D.

FDA Participants (non-voting): Robert Temple, M.D.; Russell G. Katz, M.D.; CAPT Rafel Dwaine Rieves, M.D.; Alexander Gorovets, M.D.; Qi Feng, M.D., Ph.D.

Open Public Hearing Speakers: William Thies, Ph.D..; Samantha Budd, Ph.D.; Michael Weiner, M.D.

The agenda was as follows:

8:00 a.m.	Call to Order and Opening Remarks	**Larry B. Goldstein, M.D.** Acting Chair Peripheral and Central Nervous System Drugs Advisory Committee
	Introduction of Committee	
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D., BCPS** Designated Federal Official
8:15 a.m.	FDA Introductory Remarks	**CAPT Rafel Dwaine Rieves, M.D.** Director, Division of Medical Imaging and Hematology Products (DMIHP), Office of Oncology Drug Products (OODP), OND, CDER, FDA

FDA PRESENTATION

8:30 a.m.	Overview of Potential Imaging Claims	**Alexander Gorovets, M.D.** Medical Officer Team Leader DMIHP, OODP, OND, CDER, FDA
8:45 a.m.	Clinical Presentation, Diagnosis and Management of Alzheimer's Disease	**Madhav Thambisetty, M.D., Ph.D.** Staff Clinician Section of Brain Physiology and Metabolism National Institute on Aging
9:25 a.m.	Amyloid and Amyloid Deposition in the Brain	**G. William Rebeck, Ph.D.** Associate Professor Department of Neuroscience Georgetown University Medical Center
9:45 a.m.	**BREAK**	

INDUSTRY PRESENTATION

AVID RADIOPHARMACEUTICALS

10:00 a.m.	Introduction and Development Overview of ^{18}F-AV-45	**Daniel Skovronsky, M.D., Ph.D.** CEO, Avid Radiopharmaceuticals
	Clinical Utility and Reference Standard for Amyloid Imaging	**Christopher Clark, M.D.** University of Pennsylvania, Department of Neurology Medical Director, Avid Radiopharmaceuticals
	Development Plan Proposal	**Daniel Skovronsky, M.D., Ph.D.** CEO, Avid Radiopharmaceuticals
10:30 a.m.	Clarifying Questions to Presenters	

BAYER HEALTH CARE PHARMACEUTICALS

10:40 a.m.	Introduction and Bayer Position	**Madhu Anant, M.Sc., RAC** Deputy Director, Global Regulatory Affairs Bayer Health Care Pharmaceuticals
	Clinical Utility	**Kenneth Marek, M.D.** Director, Institute of Neurodegenerative Disorders Yale University Medical School
	Phase 3 Study Design – Standard Of Truth	**Cornelia Reininger, M.D., Ph.D.** Director, Global Clinical Development Bayer Health Care Pharmaceuticals
	Conclusion	**Madhu Anant, M.Sc., RAC** Deputy Director, Global Regulatory Affairs Bayer Health Care Pharmaceuticals
11:10 a.m.	Clarifying Questions to Presenters	

GE HEALTHCARE

11:20 a.m.	Product Introduction, Proposed Indication and Clinical Development Plan for GE-067	**David Brooks, M.D., D.Sc.** Head of Neurology in Clinical Development, GE Healthcare Hartnett Professor of Neurology, Imperial College London
	Data to Support [11C]PIB as a Standard of Truth (SoT)	**William Klunk, M.D., Ph.D.** Professor of Psychiatry and Neurology University of Pittsburgh, Pittsburgh, PA
	Clinical Utility for Amyloid Imaging	**Keith A. Johnson, M.D.** Assistant Professor of Neurology, Harvard University Director of Molecular Imaging, Massachusetts General Hospital, Boston, MA
11:50 a.m.	Clarifying Questions to Presenters	
12:00 p.m.	FDA Summary and Considerations	**Qi Feng, M.D., Ph.D.** Medical Officer DMIHP, OODP, OND, CDER, FDA
12:30 p.m.	**LUNCH**	
1:30 p.m.	Open Public Hearing	
2:30 p.m.	Clarifying Questions to Presenters	
2:45 p.m.	Panel Discussion/Committee Questions	
3:30 p.m.	**BREAK**	

3:45 p.m. Panel Discussion/Committee Questions, Continued

5:00 p.m. **ADJOURNMENT**

Questions to the Committee:

1. To what extent, if any, would an indication for the use of an *in vivo* diagnostic radiopharmaceutical agent for the "detection of cerebral amyloid" provide useful clinical information?

   Committee Discussion:
   The committee discussed question #2 first before it discussed question #1. The committee agreed that a" negative" amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's Disease (AD). Additionally, the committee noted that a" positive" test would have very limited utility since cerebral amyloid is known to be present in multiple conditions, including normal aging. Hence, the clinical usefulness of a "positive" amyloid test was regarded as tenuous. Some committee members noted that a "positive" test might ultimately be useful to help characterize AD, but not to diagnose it. The committee agreed that such a test would probably be a powerful tool for future research. (See Transcript for Complete Discussion)

2. If an *in vivo* diagnostic radiopharmaceutical is clinically useful in the "detection of cerebral amyloid," what should be a "standard of truth" in phase 3 clinical studies?

   Committee Discussion:
   The committee discussed this question first, before question #1. In regards to the indication of detecting amyloid in the brain, the committee overwhelmingly agreed that histopathological correlation should be the "standard of truth" in phase 3 clinical studies. There was discussion about the feasibility of obtaining "enough" pathological studies or the ability to follow study patients to autopsy. A few committee members noted that [11C]PIB may also be a standard of truth; however, other committee members expressed concern that [11C]PIB is not an FDA-approved product and data are insufficient to establish its reliability as a marker for cerebral amyloid. (See Transcript for Complete Discussion)

3. Please comment on the strengths and weaknesses of the phase 3 study outlines supplied by the companies.

   Committee Discussion:
   The committee did not discuss this question specifically since it was agreed upon by the Review Division and the committee that the strengths and weaknesses of the phase 3 study outlines were addressed during the earlier discussions for questions #1 and #2. (See Transcript for Complete Discussion)

The meeting was adjourned at approximately 4:30 p.m.

DRAFT Regulatory and Secondary Clinical Review

Date	13 December 2010
From	Lucie Yang
Subject	Regulatory and Secondary Clinical Review
NDA	202008
Applicant	Avid Radiopharmaceuticals, Inc.
Date of Submission	17 September 2010
PDUFA Goal Date	17 March 2011
Proprietary Name / Established Name	Amyvid / Florbetapir, ^{18}F-AV-45
Dosage and Administration	370 MBq (10 mCi), intravenous
Proposed Indication	PET imaging of β-amyloid aggregates in the brain
Recommendation:	***Tentative: Complete Response***

I. Introduction

The subject of this secondary review is the New Drug Application (NDA 202008) from Avid Radiopharmaceuticals, Inc. for Amyvid (Florbetapir, ^{18}F-AV-45), a radiopharmaceutical. The product consists of a ligand targeting β-amyloid aggregates that is labeled with the radioactive isotope fluorine-18 (^{18}F). The applicant proposes that Amyvid be used with positron emission tomography (PET) to rule out the presence of β-amyloid in the brain. Individuals with clinical signs and symptoms of cognitive impairment comprise the population of intended use.

The indication statement submitted with the original application reads as follows:

> *"Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical for Positron Emission tomography (PET). Florbetapir F 18 is indicated for PET imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)."*

The sponsor subsequently modified the proposed indication statement to the following:

> *"Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain."*

The application includes a single phase 3 trial (A07) enrolling subjects into two cohorts (named "autopsy" and "specificity" by the sponsor) to address two primary endpoints. In this review, the

latter cohort will be referred to as the "young, cognitively intact (YCI)" cohort (see section 3 for explanation).

The autopsy cohort (end-of-life) subjects underwent Amyvid PET, and these images were interpreted by three readers on a 5-point scale for amyloid burden; subjects who died within one year underwent autopsy, and histopathology served as the standard of truth (SOT) for a correlation analysis.

Cognitively normal individuals younger than 40 years (the YCI cohort) also underwent Amyvid PET, and a different set of three readers evaluated these images for amyloid burden on a binary scale (+ or -) in order to determine specificity. The negative amyloid status (SOT) of the YCI subjects was presumed based on age, history and genetic testing.

This review will mainly concentrate on efficacy issues in the context of a risk / benefit assessment. Particular attention will be paid to establishing validity and reproducibility of Amyvid PET. The very small number of subjects whose PET images were read using the proposed reading method and who had histopathology as the SOT will be documented. The high degree of inter-reader variability in interpretation of Amyvid PET images will be explored.

The reviewer has examined the relevant excerpts from the NDA and additional submissions by the sponsor, as well as the primary Clinical Review and the Division of Neurology Products consult response.

II. Background / Regulatory Framework

A. Amyvid

Amyvid belongs to a class of drugs termed radiopharmaceuticals in the sense that it comprises a radionuclide that can be detected *in vivo* and a nonradioactive component that delivers the bound radionuclide to a target in the body. Some radiopharmaceuticals are used for therapy. Amyvid is not intended for therapeutic use. Importantly, as discussed below, amyloid-detecting imaging agents such as Amyvid are not intended to diagnose a disease either. Although regulations for Diagnostic Radiopharmaceuticals may be applied to Amyvid, a more accurate descriptor for amyloid-detecting agents like Amyvid may be "Nontherapeutic Radiopharmaceuticals."

Amyvid targets β-amyloid aggregates which can be found in patients with Alzheimer's Disease (AD) as well as in cognitively normal elderly individuals. Thus, simply detecting amyloid in one's brain does not diagnose AD. Although a clinicobiological lexicon for AD that does not require pathology has been proposed [1], at this point, definitive diagnosis of Alzheimer's disease requires pathological detection of both amyloid plaques and neurofibrillary tangles. These points were made very clear at the 2008 Advisory Committee (AC) meeting on clinical development of cerebral amyloid-detecting radionuclide imaging products [2].

Some may classify Amyvid as a molecular imaging agent, which is defined by the Society of Nuclear Medicine and the Molecular Imaging Center of Excellence as probes used to visualize, characterize, and measure biological processes in living systems [3]. There are no FDA

regulations strictly on the development of molecular imaging agents. However, FDA has published Guidances on developing medical imaging drugs [4-6], and recommendations in these Guidances may be applied to Amyvid.

B. Establishing Effectiveness

According to the Guidance on developing medical imaging drugs [5] and the Code of Federal Regulations (21CFR 315.5), evaluation of a drug's effectiveness entails assessment of the ability to provide useful clinical information related to its proposed indication. Four potential indication categories are: structure delineation; disease or pathology detection; functional, physiological, or biochemical assessment; and diagnostic or therapeutic patient management. A proposed indication can fall into more than one of these categories. According to the CFR, even if an imaging agent's claim does not fall into any of these categories, effectiveness of the imaging agent may still be demonstrated.

As stated above, a positive Amyvid PET test does not constitute a definitive AD diagnosis. Thus, the claim of disease detection will not be applicable to Amyvid, but pathology detection remains a possibility. For each indication category, the CFR describes what the sponsor should demonstrate to make the particular claim. For example, to claim pathology detection for an imaging agent, the sponsor should ideally demonstrate in a defined clinical setting that the drug has sufficient accuracy in identifying or characterizing the pathology.

To establish effectiveness, the Guidance also recommends that the trial demonstrate validity, reproducibility, and clinical usefulness (the latter if not already established) of the imaging agent [5]. Validity is generally evaluated by measuring performance characteristics such as sensitivity and specificity when compared to a standard of truth. In other words, the trial should demonstrate that the agent measures what it purports to measure.

Regarding reproducibility of the test result, this concept refers not only to the use of the drug in an imaging procedure, but also to the interpretation of images obtained with the use of the drug. The sponsor has expressed that Amyvid is intended to be used without incorporating clinical information. Thus, the expectation for reproducibility of Amyvid PET image acquisition and interpretation may be similar to that for certain *in vitro* diagnostic tests used in hematology or microbiology. Evaluation of reproducibility is particularly important for the Amyvid PET test.

That an imaging agent has clinical utility is important to establish because simply generating an image may not confer benefits to the patient. The clinical utility of some drugs may be self evident or established in the literature. For other agents, a trial may be necessary to demonstrate clinical utility.

C. 2008 Advisory Committee Meeting

Based on criteria for evaluating effectiveness of imaging agents set forth in the CFR and the Guidance, FDA posed questions to an Advisory Committee in 2008 regarding clinical development of radionuclide imaging agents designed to detect cerebral amyloid [7].

The first question the Agency posed to the AC was what clinical utility the detection of cerebral amyloid might have. The Committee's response was that a "negative" amyloid test could have clinical utility in ruling out AD. It was also noted that a "positive" test would have very limited utility because cerebral amyloid can be present in multiple conditions, including normal aging.

The second question FDA posed to the AC was what "standard of truth" (SOT) should be used for phase 3 clinical studies. The consensus decision was that histopathological correlation should be the SOT.

D. Histopathology Methods Used To Establish Standard of Truth

Of the various histopathology techniques for detecting cerebral amyloid, the Bielschowsky silver staining method and immunostaining with a monoclonal antibody to β-amyloid (immunohistochemistry) are the most sensitive methods for showing neuritic plaques (amyloid plus swollen, distorted axons or dendrites) [8].

According to the sponsor, automated immunohistochemistry (IHC) for amyloid is not used clinically on a routine basis due to the need for specialized equipment and training. However, IHC can provide quantitative measures of amyloid burden, with typical values generally not exceeding ~10% area occupied by amyloid.

Routine clinical assessment of amyloid burden using Bielschowsky silver staining can be used to classify neuritic plaque density into 4 categories according to the Consortium to Establish a Registry for AD (CERAD) scoring criteria [9]. These categories are none, sparse, moderate, and frequent. The latter two categories, which can be lumped together and described as "more than sparse," are consistent with AD. However, neurofibrillary tangles must also be taken into account to determine a likelihood of AD according to the National Institute of Aging (NIA) Reagan Criteria [10].

III.Efficacy

A. Phase 3 Study Design

The sponsor bases the claim of efficacy of Amyvid on the results of a single Phase 3 study (A07) titled "A Phase III study of the correlation between florbetapir F 18 (^{18}F-AV-45) positron emission tomography imaging and amyloid pathology." Study A07 enrolled two different populations to address two primary endpoints.

As recommended by the 2008 AC, histopathology correlation served to address one endpoint. Based on the AC's conclusion that a negative test could have clinical utility for ruling out AD, the sponsor also tested Amyvid PET on subjects presumed to be negative for amyloid to determine specificity as a second endpoint.

The study designs for addressing the two primary endpoints differed in many aspects including the (a) population enrolled, (b) PET image interpretation method, and (c) reference standard for amyloid burden (

Primary efficacy endpoint: For the autopsy cohort, the primary efficacy endpoint was correlation between (a) amyloid burden in the brain, at the patient level, using a semi-quantitative visual rating scale (0-4) for Amyvid PET images (median of 3 independent readers) and (b) the cortical amyloid burden by pathology using quantitative IHC. Achieving success required a statistically significant correlation (Spearman's $\rho>0$, $p\leq0.05$). For the YCI cohort, the primary efficacy endpoint was detection / exclusion of amyloid, at the patient level (majority of 3 readers). Success was defined as "specificity" $\geq$90% (95% CI: 80-98%). "Specificity" is in quotes because the standard of truth is presumed rather than demonstrated. That the YCI subjects are outside the intended use population may affect the positive predictive value.

All subjects enrolled into A07 were dosed with 10 mCi of Amyvid 50 minutes prior to PET imaging. For each endpoint, images were read by a different set of three readers blinded to clinical information. When computed tomography (CT) images of the head were obtained for attenuation correction, readers of PET images had access to these CT images.

During Phase 3 development, the sponsor has been receptive to FDA's recommendations.

Table 1).

Study population: The "autopsy" cohort comprised of adults with a projected life expectancy of $\leq$6 months. Even though there were 152 subjects in the autopsy cohort imaged, only 29 subjects were included in the primary efficacy analysis for correlation with histopathology. The "young, cognitively intact cohort" (YCI) comprised of adults equal to or younger than 40 years without risk factors for AD. The sponsor refers to this cohort as the "specificity cohort." This term will not be used in this review because the young, cognitively intact subjects are not part of the intended use population; "specificity" describes how often a test is negative only in the population of intended use for whom the target condition is absent. Of the 74 subjects in the YCI cohort imaged, only the 47 subjects who were negative for the genetic risk factor ApoE ε4 were included in the "specificity" primary endpoint analysis.

PET image interpretation method: Importantly, the PET image interpretation method for the two endpoints were different. For the autopsy cohort, PET image interpretation for amyloid burden in the cortical gray matter throughout the brain was on a 5-point scale semi-quantitative visual rating of amyloid burden (0-4, with 0 = none, 4 = high). For the YCI cohort, a binary scale was used to visually characterize amyloid status in the cortical gray matter in the entire brain as positive or negative. The YCI cohort PET images (presumably negative for amyloid) were randomized with PET images from the first 40 autopsy cohort subjects with a median (of 3 readers for the autopsy cohort) score suggestive of positive amyloid burden (2 or greater on the 5-point scale) to reduce bias.

Reference standard: Histopathology was used to unequivocally determine amyloid burden for the autopsy cohort. Patients who expired within one year of PET imaging underwent autopsy. Quantitative IHC was used to determine the average percent area occupied by amyloid averaged across six brain regions (representing a cross-section of major cortical areas). In contrast, for the YCI cohort, the reference standard was a negative amyloid status assumed based on age, history, intact memory and cognition, and absence of risk factors for AD.

Primary efficacy endpoint: For the autopsy cohort, the primary efficacy endpoint was correlation between (a) amyloid burden in the brain, at the patient level, using a semi-quantitative visual rating scale (0-4) for Amyvid PET images (median of 3 independent readers) and (b) the cortical amyloid burden by pathology using quantitative IHC. Achieving success required a statistically significant correlation (Spearman's $\rho>0$, $p\leq0.05$). For the YCI cohort, the primary efficacy endpoint was detection / exclusion of amyloid, at the patient level (majority of 3 readers). Success was defined as "specificity" $\geq$90% (95% CI: 80-98%). "Specificity" is in quotes because the standard of truth is presumed rather than demonstrated. That the YCI subjects are outside the intended use population may affect the positive predictive value.

All subjects enrolled into A07 were dosed with 10 mCi of Amyvid 50 minutes prior to PET imaging. For each endpoint, images were read by a different set of three readers blinded to clinical information. When computed tomography (CT) images of the head were obtained for attenuation correction, readers of PET images had access to these CT images.

During Phase 3 development, the sponsor has been receptive to FDA's recommendations.

Table 1. Comparison of study designs for the two endpoints in trial A07

	"Autopsy" cohort	**"Young, cognitively intact" (YCI) cohort**
Population	adults with life expectancy $\leq$ 6 months and various levels of cognitive status 152 subjects enrolled	cognitively and neurologically healthy adults $\leq$ 40 years without risk factors for AD 74 subjects enrolled
Size of primary efficacy population	n=29 died within 1 year of PET imaging mean age 80.0	n=47 no genetic risk factor for AD [ApoE ε4 negative] mean age 26.3
PET image interpretation method	5-point scale (0-4)	binary scale (+ or -)
Reference standard for amyloid burden	histopathology of subjects who died within 1 year of PET imaging specifically, quantitative immunohistochemistry (IHC) indicating % area occupied by amyloid	negative amyloid status presumed

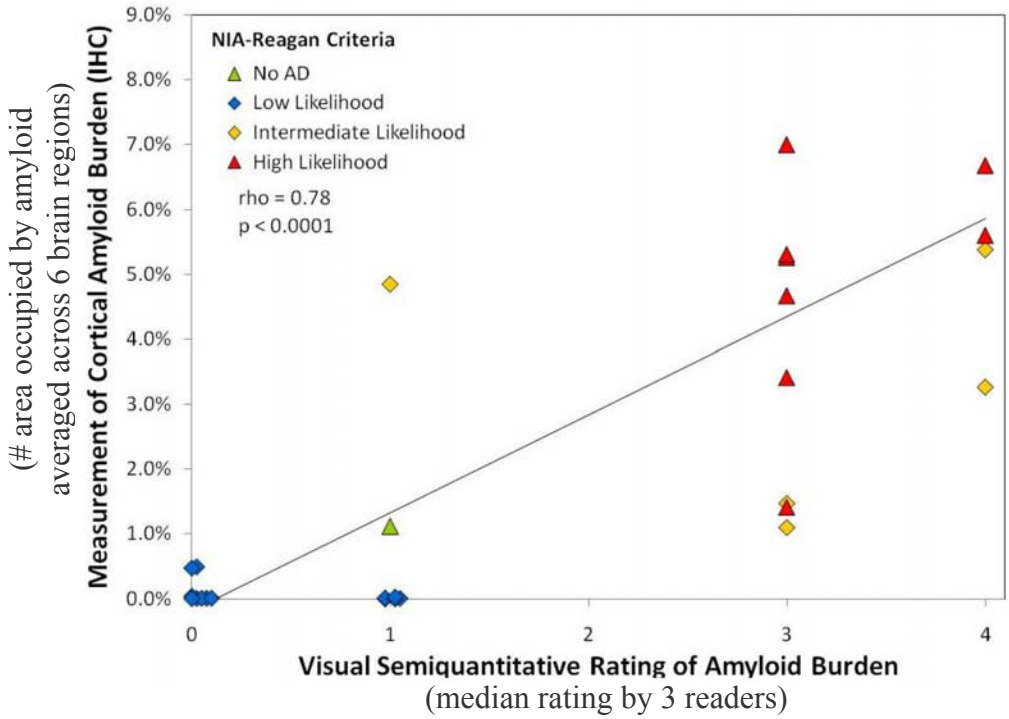
	"Autopsy" cohort	"Young, cognitively intact" (YCI) cohort
Primary endpoint / win criteria	statistically significant correlation (Spearman's $\rho > 0$, $p \leq 0.05$)	specificity $\geq$ 90% (95% CI: 80-98%)

B. A07 Results: Autopsy Cohort

Review of efficacy data for the 29 subjects in the autopsy cohort who died (and whose images were not used to refine study methods, n=6) showed that a statistically significant correlation was achieved, with Spearman's ρ=0.78, p<0.0001. Thus, the primary endpoint was met for the autopsy cohort.

Figure 1 here reproduces Figure 2 of the Clinical Review (page 25).

Figure 1. Autopsy Cohort Primary Efficacy Result.



Although the correlation is statistically significant, close examination of Figure 1 reveals that there is not an exact match between the amyloid levels established through reads of the PET images and levels determined by histopathology. For example, a median amyloid rating of 3 by the three PET readers could represent from ~1% to ~7% area occupied by amyloid. This result could in part be explained by how the PET readers were trained:

Figure 2, an excerpt from the slides used to train blinded readers in A07, illustrates that the PET image readers were informed that moderate amounts of amyloid corresponding to a rating of 2 on the 5-point scale will be rare.

Figure 2. Excerpt from Slides used for Blinded Reader Training in Trial A07

- The most important decision you will make:
  Is the patient mainly positive (3/4) or mainly negative (0/1)?
  In prior studies most subjects are either 0/1 or 3/4. It's rare to have only moderate amounts of amyloid (2).

C. A07 Results: YCI Cohort

For the YCI cohort, "specificity" was 100% for the 47 subjects who did not have the genetic risk factor for AD, ApoE ε4. Although the primary endpoint was met, there are important limitations. First, the negative amyloid status used as the reference standard was presumed rather than confirmed by pathology. Second, although the sponsor made an effort to minimize bias by randomizing PET images that were presumably positive for amyloid (from the autopsy cohort) into the image pool of the 47 YCI subjects, it is possible that reader access to structural information on CT images could have biased the interpretation of amyloid status in favor of amyloid absence for the young, cognitively healthy individuals: not only is the enrolled population not in the population of intended use, but the brains of these younger individuals (mean age 26 years) most likely show much less (if any) cortical atrophy on CT than those of the 40 autopsy cohort individuals whose PET images were added to the image pool (mean age 79 years).

D. Critique of A07 Efficacy Data

In addition to the concerns stated above, the reviewer will discuss limitations of trial A07 related to study design, sample size, and inter-reader variability.

1. Study design: Given that the 2008 AC concluded that a negative amyloid test could have clinical utility in ruling out AD, demonstrating that sensitivity is at a clinically relevant level is particularly important. Being certain that a negative result is truly a negative would give a clinician confidence that the differential diagnosis could be directed toward causes of memory impairment or cognitive decline other than AD. Demonstrating a high specificity is also important, but less so than a high sensitivity because a positive test does not definitively rule in or out any particular diagnosis. That specificity was measured in subjects outside of the population of intended use in A07 further reduces the clinical relevance of the high specificity result.

   A limitation of study A07 is that sensitivity was not an endpoint and success criteria for sensitivity was not prespecified. By adding autopsy cohort subjects presumed positive for amyloid (based on the median rating by the three readers for the autopsy cohort) into the image pool of the YCI subjects, the sponsor could calculate "sensitivity" in an exploratory manner. Importantly, the truth standard was not histopathology for 26 of these 40 subjects (which is why "sensitivity" used here will be in quotes). Using the majority read of 3 readers, "sensitivity" was reported to be 95%. Analysis by reader reveals point estimates for "sensitivity" of 85%, 93% and 95%. The caveat that access to CT images could bias the PET

read also applies here because the advanced ages of these 40 subjects predisposes them to cortical atrophy (readily apparent on CT) that is less likely in the YCI subjects.

Sensitivity can also be calculated using autopsy cohort data by transforming the semi-quantitative scale for amyloid burden on PET images into a binary scale. The sponsor defined a post-hoc threshold for amyloid burden on PET images as follows: 0-1 = amyloid absence, 2-4 = amyloid presence. For IHC results, the sponsor defined <1% as amyloid absence and >1% as amyloid presence based on comparison with the NIA-Reagan criteria for AD likelihood. Using these thresholds, sensitivity of the median PET read was 85% using IHC as the truth standard. *However, sensitivity for one of the three readers was as low as 55%* (85% and 90% for the other two readers), calling into question the validity and reproducibility of Amyvid PET. Inter-reader variability will be explored further below.

The subjects included in A07 are not representative of the intended use population. Thus, any estimates of performance characteristics are subject to spectrum bias. That being said, the 2008 AC's recommendation that histopathology should be the standard of truth raises feasibility issues for studying subjects presenting with memory impairment or cognitive decline.

2. Sample size: The applicant's proposed reading method for routine clinical use of Amyvid PET is on a binary scale (+ or – for amyloid). According to the 2008 AC, the standard of truth for a Phase 3 study of an agent designed to detect amyloid should be histopathology. *A very significant limitation of this NDA is that PET images from only 14 subjects with histopathology data were read using the proposed reading method.* With this very small sample size (all positive for amyloid), the validity and reproducibility of Amyvid PET cannot be convincingly demonstrated. For a confirmatory study, demonstration of high performance characteristics achieved by at least three readers interpreting PET images using the method proposed for routine clinical use in a much larger number of subjects would have been helpful.

3. Inter-reader variability: Another concern is that readers trained in the same manner did not necessarily produce similar interpretations for a given Amyvid PET image. Based on a detailed analysis of the rating assigned by each reader to the PET images and on performance characteristics for each reader, the Clinical Review describes the undercalling and overcalling by two readers for the autopsy cohort with respect to IHC. Only one of the autopsy cohort readers appeared to achieve both high sensitivity and specificity; according to the sponsor, this reader had previous experience assessing amyloid burden using a different imaging agent. The observations reported below regarding inter-reader variability are based on the Neurology consult response and complement those described in the Clinical Review.

   For the primary efficacy population in the autopsy cohort, the images for only 17% of the subjects (5 of 29) were rated identically by all three readers on the 5-point scale. Applying the sponsor's post-hoc thresholds for amyloid presence or absence on PET images as described above in section III.D.1. (0 or 1 as negative), in nearly ¼ of the subjects (7 of 29, 24%), at least one reader would have had a different binary interpretation of amyloid status from the other two readers (difference between highest and lowest rating $\geq$2, and lowest

rating either 0 or 1). Differences between the highest and lowest rating for PET images from the autopsy cohort are summarized in Table 2. Using histopathology as the truth standard, at least one reader would have interpreted the PET image incorrectly for 31% of subjects (9 of 29).

Table 2. Autopsy cohort rating differences among 3 readers

	Difference between highest and lowest rating among 3 readers (5-point scale from 0-4)		
	2	3	4
Primary efficacy population n=29	21% (n=6)	7% (n=2)	0% (n=0)
All subjects with ratings n=147	14% (n=21)	18% (n=27)	2% (n=3)

If all the PET images from autopsy cohort subjects (including those who did not die within 1 year of the PET imaging) were considered in a similar analysis, the images for only 25% of the subjects (37 of 147) were rated identically by all three readers on the 5-point scale. *Strikingly, in over 1/3 of the subjects (50 of 147, 34%), at least one reader would have had a different binary interpretation of amyloid status from the other two readers. Truly concerning is the observation that there were 3 of 147 subjects in which at least one reader rated the PET image as 0 (no amyloid) and at least one other reader read the same scan as a 4 (highest amyloid). For 9 of 147 subjects, at least 1 reader rated the scan as 0 for amyloid and at least one other reader rated the PET image as a 3 on a 0-4 scale.*

For the 40 autopsy cohort subjects whose images were added to the image pool of the YCI cohort, consistency in amyloid burden interpretations can be assessed across all 6 readers by transforming the 0-4 ratings by 3 readers onto the binary scale using the sponsor's post-hoc threshold. It is very concerning that for 45% of subjects (18 of 40), 1 reader differed from the other 5 readers regarding amyloid presence or absence. For 10% of subjects (4 of 40), 2 readers differed from the other 4 readers regarding amyloid presence or absence. In 5 of 40 subjects (12.5%), 1 of the 3 readers who read on a binary scale interpreted amyloid presence or absence differently from the other two readers.

Similarly, for the PET images of the 74 subjects in the YCI cohort (regardless of ApoE ε4 status), 1 reader came to a different conclusion regarding amyloid presence or absence from the other 2 readers for 11% of subjects (8 of 74).

With the variability in interpretation of Amyvid PET images described above, reproducibility and clinical utility of Amyvid PET are severely challenged.

E. Phase 1 Study A04: Test-retest Reproducibility of Amyvid PET

A Phase 1 trial was designed to assess test-retest reproducibility of Amyvid PET in cognitively normal volunteers and probable AD patients. Each subject underwent Amyvid PET imaging on 2 separate days separated by a maximum of 4 weeks. Images were read by one reader blinded to clinical information and to whether the image was a test or retest image. The single blinded reader classified images as amyloid positive or negative. Of the ten probable AD patients, the test and retest image of 1 subject was read differently (kappa 0.74). Of ten cognitively normal subjects, all test and retest images were read identically. The results of this study suggest that variability in image acquisition and display may not be significant, but the sample size was extremely small. Of note, the only difference in the interpretation of test versus retest image occurred in a probable AD subject, so it is possible that subtle differences in image acquisition or display may make a difference in determination of amyloid presence / absence for individuals who may not be cognitively intact.

F. Summary Remarks Regarding Amyvid Efficacy Data

In conclusion, the two primary endpoints in the single Phase 3 trial were met. Study A07 is commendable for successfully employing histopathology as a standard of truth. The statistically significant correlation provides some evidence of acceptable validity.

However, significant limitations in study design, sample size, and inter-reader variability cast doubt on Amyvid PET validity, reproducibility, and clinical utility. The most significant, yet rectifiable, limitation is that only 14 subjects with histopathology data had their PET images read using the proposed interpretation method for routine clinical use. The available data suggest that the variability in Amyvid PET test results more likely stems from variability in image interpretation rather than image acquisition.

This reviewer supports the opinion of the primary clinical reviewer that the efficacy data in this NDA fails to provide convincing evidence to support the efficacy of Amyvid PET for imaging β-amyloid aggregates in the brain.

IV. Safety

According to the sponsor, no safety signals have emerged for Amyvid throughout clinical trials. The applicant states that 496 subjects have been exposed to Amyvid.

V. Advisory Committee Meeting

A Peripheral and Central Nervous System Drug Advisory Committee will be convened on January 20, 2011 to consider issues of efficacy, safety, and risk to benefit ratio in the use of Amyvid for imaging β-amyloid aggregates in the brain. Validity, reproducibility, and clinical utility of Amyvid PET will be discussed.

VI. Pediatrics

Amyvid is a new molecular entity so pediatric studies have to be considered under the Pediatric Research and Equity Act. The applicant has requested a full waiver of such studies. The Pediatric and Maternal Health Staff (PMHS) has been consulted.

PMHS agrees with this reviewer and with the applicant that the waiver is appropriate.

VII. Other Relevant Regulatory Issues

The Division of Scientific Investigations is conducting good clinical practice inspections. The report is pending.

VIII. Labeling

No systematic labeling review has been performed so far in this review cycle. When approval of this application is being considered, particular attention will be paid to incorporating instructions on reader training. In addition, careful consideration will be given to the addition of "limitations of use" and to the removal of the word "diagnostic" in the indication statement.

IX. Recommendations / Risk Benefit Assessment

A. Recommended Regulatory Action

At this point in time, the regulatory and secondary clinical reviewer recommends against approving the New Drug Application 202008 for Florbetapir, 18-F AV-45 (Amyvid).

B. Risk Benefit Assessment

Although no significant risks associated with the use of Amyvid have been identified, no convincing evidence of benefit from Amyvid PET has been demonstrated either. The submitted data fail to confirm the efficacy of Amyvid for imaging β-amyloid in the brain. The inconsistency between the interpretations of amyloid presence or absence by different readers using the same images (and potential variability in image display as well) is particularly concerning. The lack of apparent benefit is accentuated by the extremely small sample size of 14 with histopathology and PET images read using the proposed interpretation method for routine clinical use. Given that clinical benefit may be conferred only by a negative test, sensitivity with pre-specified success criteria will be particularly important to assess.

C. Recommendations For Addressing Deficiencies

In conclusion, additional clinical trial data will be required to adequately demonstrate benefit for the use of Amyvid with PET. Careful consideration of the proposed reading method for PET images by the sponsor is encouraged. A third category between absolute presence and absolute absence of amyloid could be a possibility.

If the sponsor ultimately retains the binary scale (+ or -) for the proposed reading method for routine clinical use, then a re-read of the existing A07 images may be sufficient for demonstrating clinical benefit--depending on the robustness of the results. At this point, the recommendation is that PET images of all subjects who have histopathology results and the 47 YCI subjects who are negative for ApoE ε4 be included in the re-read. Pre-specified success criteria for sensitivity and specificity would be expected, with threshold values of 70% and 80%, respectively. Regarding (a) which histopathology method to use as the truth standard (for those who undergo autopsy) and (b) what threshold to use for distinguishing positive from negative amyloid burden, factors to consider include reproducibility and clinical appropriateness. The choice of standard of truth (IHC versus modified CERAD) may be reflected in the label if Amyvid is marketed. Because (a) neither of the populations in A07 truly reflect the intended patient population and (b) structural brain differences potentially evident on CT between the two study populations could bias the PET interpretation, careful consideration of whether to allow readers access to CT during the re-read is warranted. Even though regional assessment of amyloid burden may not be a part of the sponsor's proposed reading method for routine clinical use, regional sensitivity and specificity will be important for reviewer confidence in the efficacy of Amyvid. A re-read such as the one proposed above would be absolutely necessary to confirm the effectiveness of the proposed reader training methodology / materials for minimizing variability among readers prior to incorporation of training instructions into the label.

For reviewer confidence in Amyvid PET, it is recommended that a re-read separate from the one described above convincingly demonstrate agreement between interpretations by multiple PET readers who all use the same proposed method. This re-read would need to include the population of intended use such as patients with mild cognitive impairment. Because there would not be a truth standard for some subjects, results of this re-read would not be able to provide insight into correctness of the reads. Therefore, the results of this re-read may not be reflected in the label. However, demonstration of reproducibility in this manner will be necessary to support efficacy of Amyvid.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	202-008
Drug Name:	Amyvid (Florbetapir F 18 Injection)
Indication(s):	Detection of β-amyloid in the brain
Applicant:	Avid Raiopharmaceuticals, Inc.
Date(s):	Submitted date: September 17, 2010 Received date: September 17, 2010 PDUFA date: March 17, 2010
Review Priority:	Priority
Biometrics Division:	DBV
Statistical Reviewer:	Lan Huang
Concurring Reviewers:	Anthony Mucci (Acting Team Leader)
Medical Division:	Division of Medical Imaging Products
Clinical Team:	Qi Feng (reviewer), Lucie Yang (team leader), and Rafel Rieves (division director)
Project Manager:	Sharon Thomas

Keywords: Amyloid detection, open label, autopsy, reader agreement, correlation, sensitivity and specificity

Brief overview of the clinical studies

Florbetapir F 18 (formerly known as 18F-AV-45 or florpiramine F 18) is a molecular imaging agent proposed here for PET imaging of β-amyloid aggregates in the human brain. An indication for imaging of β-amyloid pathology, rather than a diagnosis of AD, is therefore sought.

The clinical development program of florbetapir F 18 comprised 6 completed clinical trials involving 496 patients: 18F-AV-45-A01 (A01), 18F-AV-45-A02 (A02), 18F-AV-45-A03 (A03), 18F-AV-45-A04 (A04), 18F-AV-45-A05 (A05), and 18F-AV-45-A07 (A07). Study A07 was the pivotal trial comparing β-amyloid levels as evaluated by florbetapir-PET imaging to post-mortem amyloid levels on histopathology.

Description of the study A07

The pivotal trial, Study A07, is an open label, single arm study. It was designed to (1) determine the relationship between measurements of brain β-amyloid using florbetapir-PET imaging and true levels of β-amyloid measured post mortem (Autopsy Cohort) and to (2) demonstrate the specificity of florbetapir- PET in a cohort of individuals unlikely to have, and therefore assumed not to have, brain amyloid plaque (Specificity Cohort). The study was conducted at 34 study centers in the United States..

The study tested two hypotheses:

Primary hypothesis #1: Correlation analysis
There is a statistically significant correlation ($\rho > 0$) between the semi-quantitative visual rating of amyloid burden of the florbetapir-PET scan and the cortical amyloid burden at autopsy as assessed by quantitative immunohistochemistry (IHC).
Spearman's Rank Order Correlation was used to assess a significant correlation.

Primary hypothesis #2: Specificity analysis
The observed specificity of florbetapir-PET imaging is ≥90% in young healthy controls.

A total of 226 subjects were enrolled in the study, 152 subjects in the autopsy cohort and 74 young healthy volunteer subjects in the specificity cohort. For the autopsy cohort, 152 subjects were enrolled from various end-of-life (e.g., hospice/hospital/nursing home) and late-life (longitudinal studies of aging) populations and yielded 35 autopsies within 1 year following the PET imaging procedure. While 35 subjects came to autopsy, the first 6 were part of a predefined front-runner study group. The subsequent 29 subjects comprised the primary autopsy analysis population.

Three independent imaging physicians (reader 1, 2, and 3) evaluated the florbetapir-PET scans in randomized blinded fashion. The neuropathology analyses were independently performed and were blinded to any clinical information, image data or reading results.

An additional cohort (specificity cohort) of young (age < 40), cognitively and neurologically healthy individuals was enrolled for specificity analysis of florbetapir-PET. The control scans were randomly mixed with scans rated positive (median rating of 2, 3 or 4) from the autopsy cohort for the blinded reading by three additional independent imaging physicians (reader 4, 5, and 6) for the specificity evaluation. The primary specificity analysis focused on the 47 controls that were not ApoE ε4 allele carriers and thus could be expected with high confidence to be devoid of brain amyloid.

Florbetapir-PET images were evaluated qualitatively (specificity cohort blinded readers), semi-quantitatively (autopsy cohort blinded readers), and quantitatively (semi-automated computerized analysis). All image evaluations and analyses were completed at the Imaging Core Lab.

For the autopsy cohort, the primary read was a visual semi-quantitative rating assessment performed by the three independent readers. Each autopsy-cohort reader rated the degree of florbetapir retention in the grey matter on a scale from 0 (no amyloid) to 4 (high levels of β-amyloid deposition), and the median score of the 3 readers (reader 1, 2, 3) was the primary efficacy endpoint.

For the specificity cohort primary (qualitative) blinded read, a new group of three readers (reader 4, 5, 6) classified images as either positive for β-amyloid (Aβ+, AD-like) or negative (Aβ-, not AD-like). The majority qualitative read result of the blinded readers was the primary efficacy endpoint for the specificity evaluation.

Note that the reading results from the two groups of reading are different, one is semi-quantitative reading with scores from 0 to 4; the other is a binary reading with score negative or positive.

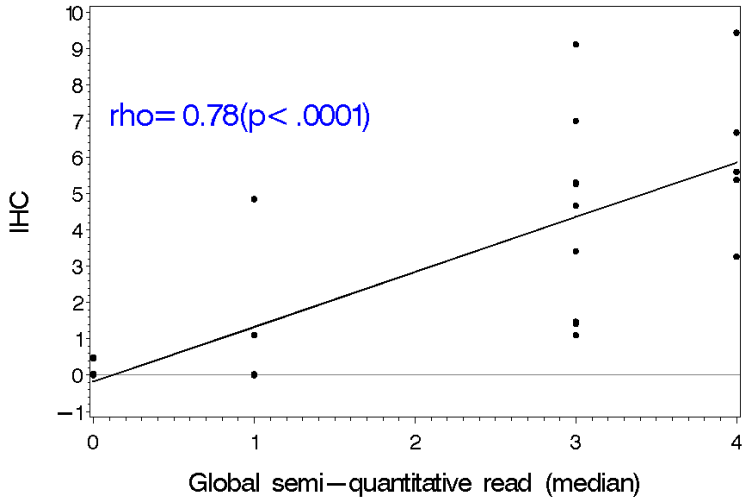
There were also several secondary quantitative (computerized) analyses:

- Correlation analyses between F-18 PET based SUVR evaluations and autopsy IHC. Note SUVR was evaluated as the mean, across six target cortical regions, of the ratios of cortical to cerebellar signal.

- Sensitivity/Specificity analyses on the 29 autopsy subjects, using the semi-quantitative scores.

Major statistical issues and findings

1. For the primary correlation analysis, a statistically significant Spearman's rho of 0.78(p<0.0001, 95% CI: 0.58 - 0.89) was observed between the median of the independent reader semi-quantitative visual ratings of amyloid detected on the florbetapir-PET image and the cortical amyloid level as assessed by quantitative IHC (average percent cortical grey matter area of β -amyloid on the IHC slides).



The results are very similar from the analysis on the 29 subjects in the efficacy population and the 35 subjects with autopsy (6 frontrunners plus the efficacy population). Therefore, sensitivity and specificity were evaluated for the 35 subjects for the two by two table with median read (semi-quantitative median read 0 and 1 as negative, and semi-quantitative median read 2, 3, 4 as positive) as the row variable and IHC category (IHC>1% as positive and IHC <1% as negative) as column variable. The sensitivity is then 85% (95% CI: 62% to 95%) and specificity is 100% (95% CI: 82% to100%).

2. To assess the variations in the individual reader performance, the correlation, and sensitivity and specificity by reader are evaluated. The Spearman's rho is 0.74 (p<0.0001), 0.74 (p<0.0001) and 0.66 (p<0.0001) for reader 1, 2, and 3 separately. For reader 1, the sensitivity is 90% (95% CI: 69%, 97%) and specificity is 100% (95% CI: 82%, 100%); for reader 2, the sensitivity is 55% (95% CI: 28%, 79%) and specificity is 100% (95% CI: 86%, 100%); and for reader 3, the sensitivity is 85% (95% CI: 64%, 95%) and specificity is 80% (95% CI: 55%, 03%). This indicates that high correlation does not imply good sensitivity and specificity, and reader performance among readers 1, 2, and 3 is very different. It is difficult to recommend clinical use of Florbetapir F 18 with only good correlation with IHC using the median read, but inconsistent reader performance.

reader	Sensitivity (%) (CI)	Specificity (%) (CI)
1	**90 (69, 97)**	**100 (82, 100)**
2	**55 (28, 79)**	**100 (86,100)**
3	**85 (64, 95)**	**80 (55, 93)**
Median read	**85 (62, 95)**	**100 (82, 100)**

3. For the primary specificity analysis, 100% (47/47) of young healthy subjects were rated as amyloid negative on the florbetapir-PET scan by the median read, which reader 4 and 6 agreeing on all 47 cases as negative, and reader 5 scoring negative on 46 of 47 cases. The observed specificity for the majority read is 100% (95% CI: 91%, 100%).

4. The subjects nearing the end-of-life were enrolled in the autopsy cohort, rather than a population of patients with cognitive impairment seeking diagnosis. The average age (SD) for the 29 subjects included for the primary efficacy analysis is 80 (SD=13). The median age is 85, maximum is 103 and minimum is 50. On the other hand, very healthy young subjects were enrolled in the specificity cohort. The average age (SD) of the 47 subjects for the primary analysis is 26 (SD=7). The median age is 24, maximum is 50, and minimum age is 18. The study population for both autopsy cohort and the specificity cohort are not representative of the intended patient population who are in middle age group with MCI.

5. The kappa statistic for the reader agreement evaluation (for the total 147 subjects with 0-4 read) is low to moderate for the autopsy cohort study (0.14 for reader 1 and 2, 0.33 for reader 1 and 3 and 0.32 for reader 2 and 3 using simple kappa; 0.54 for reader 1 and 2, 0.7 for reader 1 and 3, 0.68 for reader 2 and 3 using weighted kappa). The kappa statistic for the reader agreement evaluation (for the total 114 subjects with binary read) is high for the specificity cohort study: 0.86 for reader 4 and 5, 0.98 for reader 4 and 6 and 0.84 for reader 5 and 6. Therefore, the reader performance is more consistent in the specificity cohort study than that in the autopsy cohort study. It may be due to the difference in the reading scale, the training process, or the subjects studied. Therefore, the 100% specificity from the specificity cohort study may not be generalized to the intended patient population.

6. The primary efficacy analysis on correlation for the autopsy cohort was conducted using the 29 subjects, which is a very small sample. The correlation is statistically significantly away from 0. However, the lower bounds of the 95% CI for the sensitivity and specificity by reader are not always high. The confidence intervals are also wide. If we consider the qualitative (binary) read, only 14 autopsy subjects have binary read from reader 4, 5, and 6 in A07. And all of them have autopsy reading results as positive. It is impossible to

evaluate the sensitivity and specificity for the (binary) qualitative read using the autopsy data.

7. For the 35 subjects with autopsy, the Pearson correlation between SUVR and IHC is 0.73 ($p<0.0001$). However, this high correlation does not indicate good linear relationship between SUVR and IHC. The Pearson correlation between SUVR and IHC is 0 for subjects with SUVR <=1.1 and 0.14 for subjects with SUVR > 1.1. These discrepant results render the correlation evaluation as inadequate to assess the usefulness of quantitative reads of Florbetapir F 18 images.

Conclusions

The data from pivotal trial A07 provide statistically significant evidence that median semi-quantitaive Florbetapir F 18 image reads of amyloid burden are highly correlated with pathological read of amyloid burden. This correlation demonstrates that Florbetapir F 18 images detect amyloid deposits in the brain.

However, these data do not produce evidence of clinical usefulness of this detection since its performance characteristics (sensitivity and specificity) show considerable inconsistency among the readers for the patients from various end-of-life populations. It is not clear if this reader-to-reader variability will increase or decrease in the intended patient population. The specificity results, although consistent across readers, are obtained from the population of young healthy volunteers and again it is not clear if these results will be upheld in the intended patient population. Moreover, the sponsor has proposed using binary, qualitative read of Florbetapir F 18 images which has been applied only to 14 patients in whom pathological standard of truth was available. This sample size is too small to assess the clinical usefulness of the proposed qualitative read. The statistical review team recommends that the indication statement be modified to just state amyloid detection claim. Clinical utility of such detection will have to be assumed/inferred based on medical knowledge of the Alzheimer's disease and not from the data generated in the sponsor's Florbetapir F 18 development program.

NONCLINICAL EXECUTIVE SUMMARY

Recommendations

Approvability: Pending

Additional Non Clinical Recommendations: None

Labeling: Pregnancy category C is recommended for section 8.3 (Pregnancy) of the label.

Introduction

Amyvid (^{18}F-AV-45, Florbetapir; (E)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy) ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methylbenzenamine is proposed as a diagnostic radiopharmaceutical for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain. Amyvid selectively binds to β-amyloid plaques with high affinity. However; Amyvid demonstrates low affinity for CNS and cardiovascular receptors and monoamine transporters. Amyvid is intended for intravenous administration as a single bolus dose of 10 mCi and total volume of not more than 10 mL.

The Summary of Nonclinical Findings

1) Proof of concept Studies: *In vitro* and *ex vivo* studies were conducted to demonstrate the affinity and selectivity of Amyvid binding to β-amyloid plaque. The ability of Amyvid and other compounds to bind to amyloid plaque was evaluated in a study involving the inhibition of ^{125}I-IMPY binding in human AD brain homogenate. The study shows that Amyvid competitively inhibited ^{125}I-IMPY binding in the assay with K_i=5.5±0.7 nM as shown in Table 1.

	AV-45	PIB	FDDNP
K_i (nM) Mean ± SD	5.5±0.7	2.8±0.5	239

Table 3: Binding affinity of AV-45 and other amyloid plaque ligands to AD brain homogenates (K_i vs. ^{125}I-IMPY).

This indicates that the K_i value of Amyvid compares favorably well with those of other potential amyloid imaging agents already tested in humans.

Amyvid rapidly dissociates off the amyloid plaques after binding with a K_d value of 3.1±0.7 nM indicating that Amyvid binding to the amyloid plaques is reversible. Amyvid demonstrates high specificity in binding to its target and low binding affinity to central nervous system (CNS) and other receptor binding sites.

Autoradiography data obtained from frozen human brain sections demonstrates Amyvid labeling of β-amyloid plaques in the post-mortem brain sections of AD patients but no Amyvid labeling

was found in the brain sections of control human subjects. The data also showed that Amyvid selectively binds to the grey matters of brain homogenates of AD patients and poorly binds to the white matters of AD where amyloid β is usually low and no binding in the brain tissues of control subjects due to absence of amyloid as shown in figure 1. This indicates that Amyvid demonstrates specific binding to amyloid plaque in brain tissue.

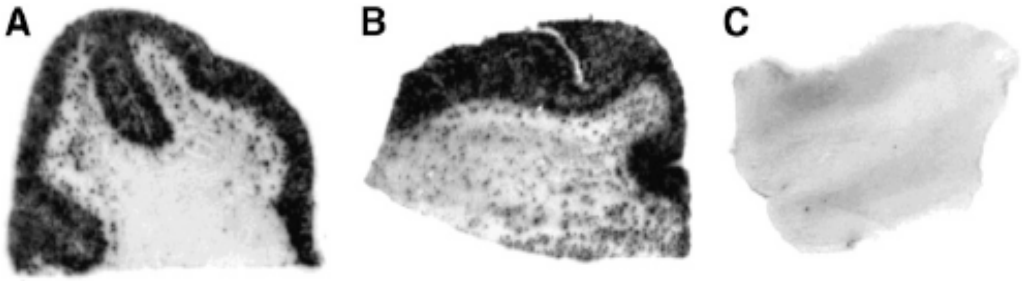


Figure 3: *In vitro* autoradiograms of frozen human brain sections labeled with ^{18}F-AV-45. (A and B) Highly intensive labeling of Aβ plaques on brain sections from AD patients. (C) Control subject exhibits no labeling by this tracer.

Transgenic mice (B6.Cg-Tg [APPswe-PSEN1]; that overexpress Aβ and generate Aβ plaques in the brain was employed as an animal model of AD to further evaluate the binding and specificity of Amyvid binding to β amyloid. There was a significant Amyvid labeling of the Aβ plaques as shown in figure 2.

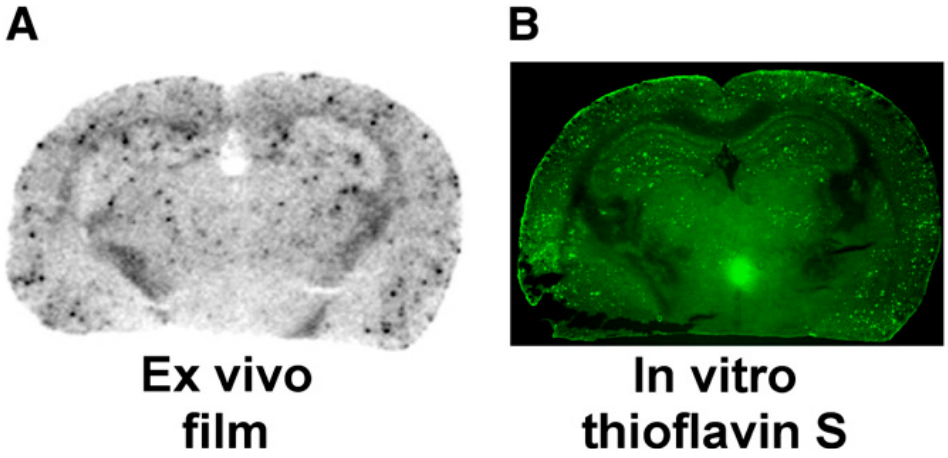


Figure 4: *Ex vivo* autoradiography of ^{18}F-AV-45 in 25-mo-old Tg (APPswe/PSEN1) mice. (A) *Ex vivo* autoradiogram of brain section. (B) Fluorescent image of comparable brain section after thioflavin S staining.

This data corroborates the binding and specificity of Amyvid to Aβ plaques in brain homogenates from AD patients in animal model of AD.

The sponsor conducted autoradiography, silver staining, thioflavin S flouresence scoring and amyloid beta specific immunohistochemistry on brain homogenates obtained from 48 human

brain tissues. Correlation analysis performed on Amyvid binding and the data obtained from the studies indicates:

a) Correlation between Amyvid binding and neuritic plaque scores.

b) Correlation between Amyvid binding and β-amyloid plaque deposition measured by silver stain, anti-Aβ immunohistochemistry (using two different antibodies), and thioflavin S staining as shown in figure 3

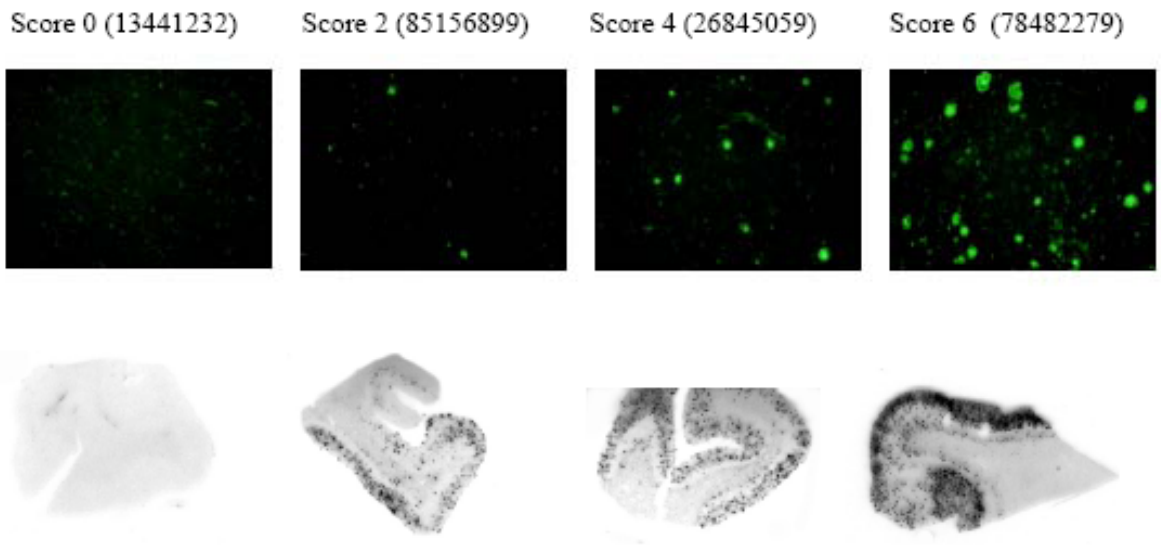


Figure 3: Thioflavin S staining and scoring. The figure shows representative sections. Scores used were 0:none, 2:spare, 4:moderate and 6:frequent thioflavin S- positive aggregates (numbers in brackets correspond to subjects numbers in the Table below). The autoradiographs in the second row show the corresponding ^{18}F-AV-45 binding.

and

c) Correlation between Amyvid binding and immunohistochemistry quantification obtained using specific Aβ antibodies.

2) Pharmacokinetics, Distribution and Excretion: The autoradiographic and biodistribution data obtained from mice and Rhesus monkey indicate that following an intravenous injection, Amyvid penetrates the brain readily and is rapidly cleared from the brain. The rapid clearance reduces non-specific binding to the brain tissue which could complicate imaging. The dosimetry data showed an estimated human effective dose of 97 mrem/mCi, which is within acceptable radiation dose limit. This indicates that no radiation toxicity is envisaged during the administration of Amyvid at the intended dose. Amyvid metabolism was studied using human and rat liver microsomes in the presence of an NADPH-generating system. The data showed that Amyvid is demethylated to AV-160 and subsequently acetylated to AV-267. The binding

characteristics of these metabolites to beta amyloid plaques were evaluated using autoradiography. Both metabolites demonstrate low affinity to the beta amyloid plaques. This indicates that the metabolites will probably not interfere with Amyvid binding. Amyvid and the metabolites are excreted from the body via urinary route.

3) Safety Pharmacology Studies: The CNS safety of Amyvid was evaluated in single/repeat-dose toxicity study in Sprague Dawley rats. No CNS adverse effects were reported in single or 28-day repeated dosing at up to 21.8X MHD dose levels. Potential cardiovascular effect of Amyvid was assessed using both *in vitro* and *in vivo* studies. Amyvid inhibited hERG potassium current by 16.7±0.9% (n=4) at 12.4 μM; the only employed dose due to solubility problem, verses 0.2±0.1% (n=3) in control while the reference positive control, terfenadine (60nM), induced up to 83.8% inhibition on the hERG cells. Adverse cardiovascular or respiratory effects were not observed following Amyvid treatment of up to a dose of 84X MHD in a cardiovascular safety pharmacology and respiratory function study in beagle dogs.

4) Toxicity Studies: Single- and repeat-dose toxicity studies were conducted in rats and Beagle dogs. No treatment-related mortality or any serious adverse effects was reported in any of these studies. NOAELs of 87.2X- and 21.8X- MHD were obtained in a single- and 28-day repeat-dose toxicity study respectively in the rats. No cardiovascular or ocular effects were reported during 14-day repeat-dose toxicity study with a 2-week recovery conducted in Beagle dogs and a NOAEL of 4.5X MHD was obtained. A NOAEL of 21X MHD was obtained during 28-day repeat-dose toxicity with 14-day recovery period conducted in Beagle dogs

5) Reproductive Toxicity Studies: No reproductive toxicity study was conducted on Amyvid. However, the sponsor's request for a waiver for reproductive and developmental toxicity studies was granted. Pregnancy category C is recommended for label.

6) Genotoxicity Studies: The standard ICH battery of tests including two *in vitro* assay covering the bacterial reverse mutation assay (Ames test) and chromosomal effects (cultured human peripheral lymphocytes cells) was evaluated. Amyvid tested positive to *in vitro* assays and negative during *in vivo* mouse micronucleus assay. This data would be reflected in the label.

7) Carcinogenicity Studies: No carcinogenicity study was conducted on Amyvid. The sponsor's request for a waiver for carcinogenicity studies was granted.

8) Impurities: Impurities were quantified and found to be within acceptable limits.

9) Nonclinical safety issues relevant to clinical use: The available nonclinical findings do not show any significant nonclinical safety issues that could adversely affect the clinical use of Amyvid in the context of its proposed indication in this NDA.

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10) Conclusions: Based on the review of the preclinical data, there seems to be no significant safety concerns with Amyvid and the proposed indication.

The DRAFT Clinical Review begins on the following page/to preserve pagination.

DRAFT CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-008
Priority or Standard	Priority
Submit Date(s)	September 17, 2010
Received Date(s)	September 17, 2010
PDUFA Goal Date	March 17, 2011
Reviewer Name(s)	Qi Feng, MD, PhD
Review Completion Date	October 4, 2010
Established Name	Florbetapir, 18-F AV-45
(Proposed) Trade Name	Amyvid
Therapeutic Class	Diagnostic molecular imaging agent
Applicant	Avid Radiopharmaceuticals, Inc.
Formulation(s)	370 MBq (10 mCi) florbetapir F 18 in 10% (v/v) ethanol, 0.45% (w/v) sodium ascorbate, 0.81% (w/v) sodium chloride sterile aqueous solution, at a strength of 37-1900 MBq/mL (1-50 mCi/mL) per unit dose vial or syringe at the time of calibration.
Dosing Regimen	370 MBq (10 mCi)
(Proposed) Indication(s)	*"Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain."* (as proposed on 11/23/2010)
Intended Population(s)	Adult patients with cognitive dysfunction

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Abbreviations and Definition of Terms

AD: Alzheimer's disease
AE: adverse event/adverse experience
ApoE: Apolipoprotein E
CERAD: Consortium to Establish a Registry for Alzheimer's Disease
CFR: Code of Federal Regulation
CI: confidence interval
CMC: Chemistry Manufacturing and Controls
CT: computed tomography
F-18: fluorine-18
F-19: fluorine-19
FDG: fluorodeoxyglucose (F-18)
g: gram
GCP: Good Clinical Practice
IHC: immunohistochemistry
IND: Investigational New Drug
IV: intravenous
HC: healthy control
KeV: kilo-electron volt
MBq: megabecquerel
mCi: millicurie
mg: milligram
MHD: maximum human dose
mL: milliliter
MRI: magnetic resonance imaging
mSv: millisievert
NDA: New Drug Application
NOAEL: no observable adverse effect level
NPV negative predictive value
PET: positron emission tomography
PiB: Pittsburgh compound B
PPV positive predictive value
rho: Spearman's rank correlation coefficient
SAE: serious adverse event
SOT: standard of truth
SUV: standard uptake value
SUVR standard uptake value ratio
TEAE: treatment-emergent adverse event
µg: microgram

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to FDA guidelines on regulatory expectations for diagnostic radiopharmaceutical agents, phase 3 clinical trial data should demonstrate clinical utility (if not already established), test validity and reproducibility [1, 2] in order for an imaging agent to be approved. Based on these criteria and the tentative review findings, at this time the clinical reviewer does not recommend approval of NDA 202-008 for Amyvid (Florbetapir F-18 Injection) for the indication of amyloid detection in the brain with a PET scan. This preliminary recommendation is based on review of the efficacy data from the NDA submission, mainly from the single pivotal phase 3 clinical trial for 18-F-AV-A07, A07. The recommendation is not based upon the submitted safety data.

At this time, the reviewer recommends that the sponsor design and conduct the following study in order to demonstrate validity and reproducibility of Amyvid PET:

> Re-read the PET images from A07, including at least the 82 subjects (35 subjects with autopsy and 47 young, cognitively normal subjects from the "specificity cohort"), by three new independent readers with a single review charter using the proposed visual interpretation method on a binary scale (+ or —) in order to validate performance characteristics, and to assess inter-reader variability and reproducibility of Amyvid PET.

1.2 Risk Benefit Assessment

To date, Amyvid does not have an acceptable risk benefit assessment. Rationale is as follows:

1. Small sample size (n = 14) to validate the proposed image interpretation methodology in subjects with amyloid status confirmed by histopathology

2. High inter-reader variability for PET image assessment among the three blinded readers in the autopsy cohort

3. No clear clinical utility is demonstrated in the phase 3 trial (whether utility is self-evident or established for brain amyloid imaging will be discussed at the advisory committee)

4. Phase 3 trial subjects were not the population of intended use. If marketed, Amyvid would likely have a relatively broad target patient population (adults with cognitive deficit) in the real world, and these subjects were not tested in the Phase 3 trial

5. Wide range of true amyloid burden by immunohistochemistry for some PET ratings (median of three readers) of amyloid status.

1.3 Recommendations for Postmarket Risk Management Activities

None at the present time.

1.4 Recommendations for Postmarket Studies/Clinical Trials

None at the present time.

2 Introduction and Regulatory Background

2.1 Product Information

Alzheimer's disease (AD) is the most common form of dementia in individuals over 65 years of age. In the early stages, the most commonly recognized symptom is inability to acquire new memories, such as difficulty in recalling recently observed facts. When AD is suspected, the diagnosis is usually confirmed with behavioral assessments and cognitive tests. As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and general withdrawal of the sufferer as his/her senses

decline. According to the Alzheimer's Association's "2009 AD Facts and Figures," 5.3 million Americans are living with AD [3].

The definition of Alzheimer's disease is undergoing evolution. Although a clinicobiological lexicon for AD has been proposed, at this time, AD can only be definitively diagnosed by post-mortem pathology. Clinically, AD is usually diagnosed as “probable AD” or “possible AD” based on the presence of characteristic neurological and neuropsychological features (cognitive dysfunction, dementia), patient history, family history, and the absence of alternative conditions. Multiple studies have showed that clinical diagnosis is imperfect, with approximately 81% sensitivity (range 49 to 100%) and 70% specificity (range 47 to 100%) when the gold standard is pathology at autopsy [4]. Currently, imaging modalities such as CT, MRI and FDG PET/CT are primarily used to help exclude other cerebral pathology or subtypes of dementia. To date, there is no approved treatment or medication which consistently delays or reverses AD progression after diagnosis.

The risk factors for AD include age (> 65 yrs old), heredity (first degree relatives, parents, sister and brothers), sex (female more likely), mild cognitive impairment, lifestyle (hypertension, hypercholesteremia and diabetes), and less education. One genetic risk factor is apolipoprotein E (ApoE) ε4 on chromosome 19, which occurs in about 40% of all individuals who develop late-onset AD.

The exact cause and progression of AD are not well understood yet. Research suggests that the disease is associated with plaques (primarily composed of beta amyloid peptides) and neurofibrillary tangles in the brain. The AD pathology diagnosis requires presence of both amyloid plaques and neurofibrillary tangles.

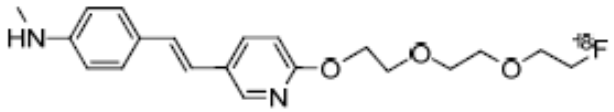
Amyloid consists of insoluble fibrous protein aggregates. Abnormal accumulation of amyloid in organs may lead to amyloidosis or play a role in various neurodegenerative diseases, including AD, Parkinson’s disease, transmissible spongiform encephalopathy, Huntington’s disease, familial amyloid polyneuropathy and cerebral amyloid angiopathy [5, 6, 7, 8, 9].

Pittsburgh compound B (PiB), a fluorescent analog of thioflavin T, can bind beta-amyloid plaque in post-mortem brain tissue in *in vitro* studies, suggesting the potential for use as a PET tracer for amyloid detection in the brain [10].

Amyvid is a radiopharmaceutical tracer and the non radioactive ingredient of the drug is an analog of PiB. The radioactive isotope of the drug is fluorine-18, which decays by positron emission with a half-life of 110 minutes.

Amyvid comprises of 370 MBq (10 mCi) florbetapir F-18 in 10% (v/v) ethanol, 0.45% (w/v) sodium ascorbate, 0.81% (w/v) sodium chloride sterile aqueous solution, at a strength of 37 - 1900 MBq/mL (1 - 50 mCi/mL) per unit dose vial or syringe at the time of calibration.

The chemical name of Amyvid is (*E)-4-(2-(6-(2-(2-(2- [18F]fluoroethoxy)ethoxy)ethoxy) pyridin-3-yl)vinyl)-N-methylaniline* which has the following structure:



The molecular formula of the drug is $C_{20}H_{25}$[18-F]N_2O_3 and its molecular mass is 359 atomic mass unit.

On October 23, 2008, FDA convened a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (AC) to discuss strategies for clinical development of PET tracers designed to detect amyloid. One question posed by FDA was, "*To what extent, if any, would an indication for the use of an in vivo diagnostic radiopharmaceutical agent for the "detection of cerebral amyloid" provide useful clinical information?"* The committee agreed that a negative amyloid test could have clinical utility in ruling out a diagnosis of AD. Additionally, the committee noted that a positive test would only be supportive in the diagnosis of AD and would not provide a definitive diagnosis. A second question posed by FDA was, " *If an* in vivo *diagnostic radiopharmaceutical is clinically useful in the "detection of cerebral amyloid," what should be a "standard of truth" in phase 3 clinical studies?* " Here the committee

overwhelmingly agreed that histopathological correlation should be the "standard of truth" in phase 3 clinical studies [11]. The crux of the Amyvid NDA is a Phase 3 histopathological correlation, and this data is the main focus of the NDA review.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there is no approved imaging agent in the United States for detection of amyloid in the brain.

2.3 Availability of Proposed Active Ingredient in the United States

Amyvid is a new molecular entity and it is not currently marketed in the United States.

If approved, Amyvid will be manufactured by Avid Radiopharmaceuticals Inc. at multiple facility sites. The drug is a conjugate of the Florbetapir F-19 molecule (19-F is the stable isotope of element fluorine), with radioisotope 18-F replacing 19-F in the conjugation process. The final precursor, Florbetapir 19-F, is manufactured by Girindus America, Inc., 8560 Reading Road, Cincinnati, OH 45215, USA. The manufacturing of Amyvid (Florbetapir 18-F) is performed by 19 facility sites of Cardinal Health, Inc (8) and PETNET Solutions (11) throughout the United States. All starting materials, reagents, solvents and other materials used for the manufacturing of the drug are controlled and released according to Avid specifications prior to use.

2.4 Important Safety Issues with Consideration to Related Drugs

Amyvid is a compound with the radioactive isotope F-18. Radiation safety concerns are present secondary to positron emission of gamma radiation (photon energy of 511 KeV) by the F-18 radioisotope. The reported effective dose of 7.03 mSv for a 10 mCi dose of Amyvid represents an acceptable level of radiation exposure to the human subject given that guidelines for radiation workers recommend a maximum exposure limit of 50 mSv per year [12]. A 10 mCi Amyvid dose is in the lower range of radiation effective dose for general nuclear medicine imaging procedures.

It is not known whether Amyvid is excreted into human milk. Therefore, a decision regarding the duration for which to interrupt nursing (generally at least 5 times the half-life of the specific

radioisotope in order to minimize risks to nursing infants) following drug administration should be made by the patient's physician.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The regulatory history of the NDA:

1. 01/08/2007: Exploratory IND 76-852 was filed and withdrawn on 02/14/2008
2. 03/06/2008: Pre-IND and then IND 79-511 was filed
3. 10/23/2008: AC Meeting held to discuss clinical development of PET tracers for the detection of amyloid
4. 11/03/2008: Type-C meeting to reiterate AC recommendations regarding the use of histopathology as the standard of truth
5. 02/11/2009: Type-C meeting to discuss "autopsy" and "specificity" cohorts proposed for the phase 3 trial
6. 04/13/2010: Reproductive toxicology waiver was requested by the sponsor
7. 07/26/2010: Carcinogenicity testing waiver was requested
8. 03/09/2010: Pediatric testing waiver was requested
9. 06/17/2010: Priority review was requested
10. 07/19/2010: Type-B Pre-NDA meeting
11. 09/17/2010: Submission of NDA 202-008 Amyvid
12. 10/07/2010: Sponsor presented NDA to FDA review division
13. 11/15/2010: Sponsor's second presentation of NDA to FDA review division
14. 11/23/2010: Type-B meeting during which the sponsor specified that a binary (positive/negative amyloid) image interpretation methodology was the intended reading method for Amyvid PET images in clinical practice. Sponsor proposed a new indication and label.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

To date, the data quality and integrity of the phase 1, 2 and 3 trials submitted appear acceptable according to regulatory expectations.

The Division has consulted the Division of Scientific Investigations (DSI), Center for Drug Evaluation and Research, FDA regarding site inspections for the NDA. Study sites were selected for inspection based upon the following reasons:

1. The study was considered as the most important for efficacy and safety claims (A07).
2. The number of subject enrolled at the sites exceeded the average number of patients enrolled in the study.
3. The sites with more protocol deviations compared to other sites.

The DSI site inspection report is pending and may impact the data quality/integrity assessment.

3.2 Compliance with Good Clinical Practices

Based on the sponsor's statement at the beginning of each clinical report, the studies were conducted in full accordance with the Declaration of Helsinki; the International Conference on Harmonization (ICH) consolidated guideline E6 - Good Clinical Practice (GCP) and any applicable national and local laws and regulations.

3.3 Financial Disclosures

According to the submission, the A07 study was conducted at 34 study centers in the United States, 25 of which enrolled at least 1 subject (range from 1-25 subjects). Principal investigators at these 25 sites had financial disclosures in the submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls (CMC) review is pending. At this time, no issues that might affect efficacy or safety have been reported.

4.2 Clinical Microbiology

No issues to report at this time.

4.3 Preclinical Pharmacology/Toxicology

In vitro binding studies showed high amyloid binding affinity of Amyvid to amyloid without significant cross reactions to the prevalent central nervous system (CNS), peripheral nervous system (PNS) or cardiovascular receptors. No adverse effects of the non-radioactive form of the drug on the CNS were observed in the standard functional observational battery test up to 100X the intended maximum human dose (MHD) in rats.

An acute dose study was conducted in rats, and the NOAEL (no observable adverse effect level) was determined to be at least 100 times MHD. The potential toxicity of 28 days of repeated IV injections of the drug was tested in rats and Beagle dogs, and the NOAEL was found to be at least 25x the MHD.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Amyvid binds to amyloid plaques in human brain tissue obtained post-mortem from subjects with AD pathology. In equilibrium binding studies using homogenates of AD brain tissue, the dissociation constant for florbetapir was measured at K_d = 3.7 nM. The binding was visualized in brain sections from subjects with AD pathology with autoradiographic methods. Positive

staining was observed in gray matter of post-mortem AD brains, but not in control tissue from subjects without AD pathology. Amyloid deposition was assessed using neuropathological staining procedures, including Bielschowsky silver staining and immunohistochemistry with anti-amyloid antibodies. *In vitro* studies demonstrated correlations between drug binding and amyloid deposition.

4.4.2 Pharmacodynamics

The radioactive imaging signals generated by Amyvid, which can be measured by standard uptake value (SUV), were visible from 30 to 90 minutes postdose. The images from 30 - 40 minutes and 50 - 60 minutes postdose showed good agreement by the blinded readers, suggesting the window of time for imaging after tracer injection.

The test-retest reproducibility study (A04) result showed good intra-class correlation and low test-retest variability. A comparison of a 10 minute versus a 20 minute scan acquisition period showed no difference in radioactive signals. Therefore, a 10 minute PET scan is recommended for the imaging for reasons of patient comfort and compliance.

4.4.3 Pharmacokinetics

Amyvid bio-distribution study A02 showed that the drug was rapidly distributed throughout the body following IV administration. Rapid clearance from circulation and localization in the liver/GI system was observed. Images over time show that elimination occurs primarily by way of clearance through the liver and excretion into the gallbladder and the intestines. Some accumulation/excretion is also observed in the urinary bladder. The drug is very rapidly cleared from circulation postdose. Less than 5% of the injected radioactivity remains in blood by 20 minutes following administration.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 summarizes all studies submitted in the NDA:

Table 1: All Studies Submitted in the NDA

Phase	Study ID	Subjects # (n)	Objectives
1	A01	32	PK
	A02	9	Dosimetry
	A03	20	Dose (3 vs. 10 mCi)
	A04	25	Test-retest
	A06	41 (re-read of select A01 and A03 images)	Timing for imaging
2	A05	184	Imaging profile, safety
3	A07	226	PET-pathology correlation, specificity
		Total 496	

5.2 Review Strategy

The clinical reviewer will verify, evaluate and analyze all data submitted related to the efficacy and safety claims of Amyvid. There were seven studies in total, including five phase 1 studies, one phase 2 study, and one phase 3 study. Because there is only one pivotal phase 3 trial (A07) and this was the only trial in which histopathology was used as the standard of truth (SOT),--as requested by 2008 AC members--the reviewer will primarily and extensively concentrate on this trial. The review includes detailed data verification, dissection and analysis of the primary and secondary endpoint data, as well as critiques of the weaknesses in trial design, data and conclusions claimed. For the drug safety review, the reviewer will assess data from all 7 trials submitted in the NDA. A total of 496 subjects received at least 1 dosing of the drug.

For efficacy, the clinical review assesses the sponsor's results using Spearman's rank correlation coefficient (rho), sensitivity, specificity, positive predict value (PPV), negative predictive value (NPV) and accuracy. The lead statistical reviewer, Dr. Lan Huang, is actively involved in raw data verification and analysis.

6 Review of Efficacy

6.1 Indication

In the original NDA submission, the proposed indication was:

> "*Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)"*

After several discussions with the FDA, the sponsor has revised the proposed indication to:

> "*Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain."*

Reviewer comments: "……significant levels of β-amyloid in the brain" might be misleading or not be specific enough. It might be necessary to add "**(more than sparse neuritic plaques by the CERAD rating)"** after the "……significant levels of β-amyloid in the brain" to more precisely specify the amyloid level detected so that clinicians may have a better understanding of what a negative Amyvid PET scan suggests.

6.2 Efficacy Summary

The Amyvid efficacy results are mainly from the "autopsy" and "specificity" cohorts of trial A07.

1. In the only Phase 3 trial for this NDA (A07), only 14 subjects had (a) PET images read using the sponsor's proposed reading method for routine clinical use (positive or negative for amyloid) and (b) histopathology as a standard of truth. This small sample size is a significant limitation of this NDA.

Three different visual rating methods were used to evaluate amyloid burden on PET images in the A07 trial. First, a 5-point scale (0-4) was used for the autopsy cohort. Second, a binary rating scale (+ or -) was used for PET images of the young, cognitively normal subjects (and the 40 autopsy cohort subjects added to reduce bias). Both of these scales were applied to estimate amyloid burden in gray matter across the whole brain (global). A third visual rating method (3-point scale from 0-2) was used to evaluate the amyloid burden in each of 6 regions of the brain (regional); according to the sponsor, this information was not used in any analysis. In a meeting on 11/23/2010, the sponsor informed FDA that the intended reading method for routine clinical use of Amyvid PET scans is a binary (+ or -) scale. As stated above, PET images from only 14 subjects who had histopathological confirmation of amyloid status were read using this binary scale.

PET images read on the 5-point was converted to a binary scale on a post-hoc basis by the sponsor to calculate performance characteristics (sensitivity, specificity). Importantly, the thresholds for designating a PET scan as positive or negative based on the 5-point scale were not prespecified and prospectively tested.

2. For the autopsy cohort, the sponsor reports a statistically significant Spearman's correlation (rho = 0.78, $p < 0.0001$) between the median semi-quantitative 5-point visual rating of the PET image by three blinded readers and the percent cortical gray matter area occupied by amyloid assessed using quantitative IHC . Therefore, the primary endpoint for this cohort was met. However, detailed analysis of individual reader rating of amyloid burden on PET images demonstrates that the median rating obscures the high inter-reader variability among the 3 readers. This observation suggests low reproducibility of visual rating across readers. In addition, there is a wide range of true amyloid burden by IHC for some median PET ratings.

3. For the cohort of young, cognitively normal subjects without known genetic risk factors for AD (termed "specificity cohort" by the sponsor), high specificity (100%) of the majority read by three readers blinded to clinical information was demonstrated.

Importantly, the negative amyloid status (the standard of truth for this cohort) was presumed rather than confirmed by histopathology. These PET images were read as positive or negative for amyloid. As stated above, this binary reading scale is the sponsor's proposed reading method for Amyvid PET images in routine clinical use.

For the read sessions of PET images of the young, cognitively normal subjects, additional PET images from 40 autopsy cohort subjects with a median rating on PET images suggestive of amyloid positivity were randomized into the reading queue to minimize bias. Of these 40 autopsy cohort PET images, only 14 had histopathology confirmation. An additional concern is that CT images of some subjects were available to the PET image readers. The reason for this concern is that structural information gleaned from CT images could introduce bias into a reader's decision on amyloid presence or absence based on PET images: young, cognitively normal subjects with a mean age of 26 years would unlikely demonstrate the cortical atrophy that autopsy cohort subjects with a mean age of 80 years may.

4. There was a statistically significant Spearman's correlation (rho = 0.68–0.75, $p<0.0001$) between the semi-quantitative visual ratings of amyloid burden on the PET image for each of 6 cortical regions and the percent area occupied by amyloid measured by quantitative IHC.

5. The subjects in the A07 trial did not represent the population of the intended use. The relatively small sample size of the autopsy cohort reflects the challenges associated with conducting a study requiring histopathology of autopsy specimens as the standard of truth.

6.3 Methods

The methods described in this section were used in the A07 trial unless otherwise specified. The objective of the trial is to assess the relationship between measurements of amyloid with Amyvid PET imaging and true levels of amyloid burden assessed by histology at autopsy. For the

autopsy cohort, 152 subjects were enrolled from various end-of-life (hospice/hospital/nursing home) and late-life populations. In order to evaluate the specificity of the drug for detecting the absence of amyloid, a separate cohort of 74 young, cognitively normal and neurologically healthy subjects was enrolled for imaging only. For the latter cohort, the absence of amyloid was presumed.

1. Amyvid dose, image acquisition, safety follow-up: Each subject received a single IV injection of 370 MBq (10 mCi) Amyvid, followed by a saline flush. Image acquisition for 10 minutes occurred around 50 minutes postdose. Subjects were followed up for safety evaluation for 48 hours postdose.

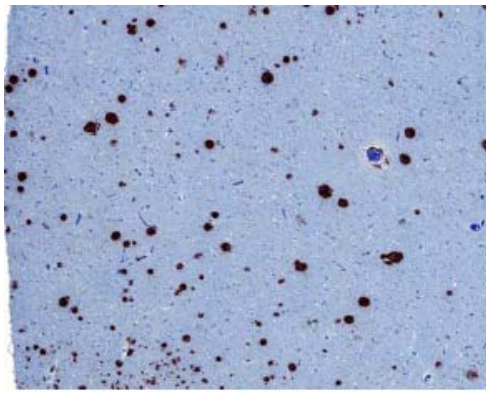
2. PET imaging assessment: For the autopsy cohort, 3 readers blinded to clinical information (readers 1, 2, 3) evaluated images at the imaging core lab (Image Metrix). The readers rated each image for overall cortical amyloid burden on a 5-point scale, ranging from 0 (no amyloid) to 4 (high levels of amyloid). Readers provided both global and regional ratings of amyloid deposition. Of the 35 autopsy subjects, 29 were included in the primary endpoint analysis; the 6 "front runners" were used to finalize study methods. In order to calculate performance characteristics, the semi-quantitative 0-4 rating was converted to the binary scale using the post-hoc threshold of 1 or lower as negative and 2 or higher as positive.

   For the young, cognitively normal cohort, PET images were assessed by three different readers (readers 4, 5, 6) on a binary scale (+ or –) for amyloid in the gray matter of the whole brain (global) for the primary endpoint. For an additional objective, readers rated the images on a 3-point scale (0 for no amyloid, to 2 for high levels of amyloid) for three regions of the brain (regional).

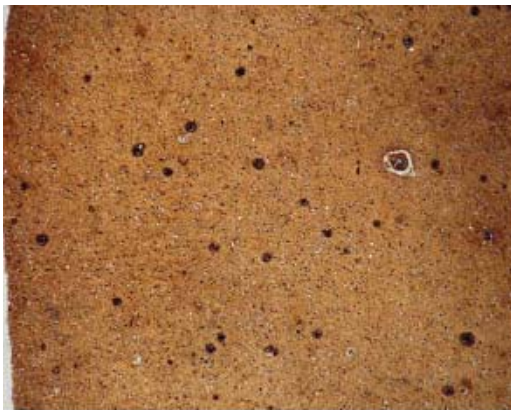
3. Brain autopsy preparation performed by Sun Health Research Institute (Sun City, AZ): Brain autopsy tissue blocks were dissected into 1 cm^3 sections for each of 7 regions,

including 6 regions from the cerebrum (frontal, temporal, parietal lobes, precuneus, anterior cingulate, posterior cingulate) as well as the cerebellum.

4. Immunohistochemistry (IHC) performed by Biospective, Inc. (Montreal, Canada): The brain tissue slides were stained using 4G8 monoclonal anti-amyloid antibody as the primary antibody. Pictures of the final slides were digitized and fully automated for quantitating % area occupied by amyloid. A representative picture is on the right:



5. Bielschowsky silver stain performed by Rush University Medical Center (Chicago, IL): Brain tissue slides were stained using the modified Bielschowsky silver staining protocol. A representative picture is on the right. Neuritic plaques were counted by 2 independent readers and then reviewed by a neuropathologist whose plaque count could replace those of the two independent readers. All 3 readers were blinded to the subject's clinical information, PET imaging result and IHC result.



6. Table 2 illustrates a method to convert from the modified Bielschowsky silver stain neuritic plaque counts to the modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque rating scale. At the 11/23/2010 meeting with FDA, the sponsor proposed that the 4-point CERAD neuritic plaque rating scale could be made binary (sparse or none classified as negative) and be used as a truth standard to calculate performance characteristics. Importantly, the A07 Phase 3 trial did use of this method for the truth standard for the primary endpoint.

Table 2: Conversion from Silver Stain Result to CERAD Scale for Neuritic Plaque Counts

Highest Neuritic Plaque Counts	CERAD Neuritic Plaque Scale
0	None
1 – 5	Sparse
6 – 19	Moderate
≥ 20	Frequent

6.4 Demographics

Table 3 summarizes the demographics of the A07 trial:

Table 3: A07 Trial Demographic Characteristics by Cohort*

Characteristic	Autopsy Cohort		Specificity Cohort	
	Subjects Imaged N=152 [a]	Subjects with Autopsy N=29 [b]	Subjects Imaged N=74 [a]	Non-ApoE ε4 Carriers N=47 [b]
Age (years)				
Mean ± SD	78.1 ± 13.35	80.0 ± 13.19	26.6 ± 6.50	26.3 ± 7.17
Median	81.5	85.0	25.5	24.0
Range	38 to 103	55 to 103	18 to 50	18 to 50
Gender				
Male	71 (46.7%)	15 (51.7%)	48 (64.9%)	32 (68.1%)
Female	81 (53.3%)	14 (48.3%)	26 (35.1%)	15 (31.9%)
Race				
Caucasian	134 (88.2%)	26 (89.7%)	57 (77.0%)	36 (76.6%)
Black or African-American	10 (6.6%)	2 (6.9%)	6 (8.1%)	4 (8.5%)
Other	4 (2.6%)	1 (3.4%)	7 (9.5%)	4 (8.5%)
Asian	2 (1.3%)	0	4 (5.4%)	3 (6.4%)
Native American / Alaskan Native	2 (1.3%)	0	0	0
Ethnicity				
Non-Hispanic or Latino	139 (91.4%)	28 (96.6%)	69 (93.2%)	44 (93.6%)
Hispanic or Latino	13 (8.6%)	1 (3.4%)	5 (6.8%)	3 (6.4%)

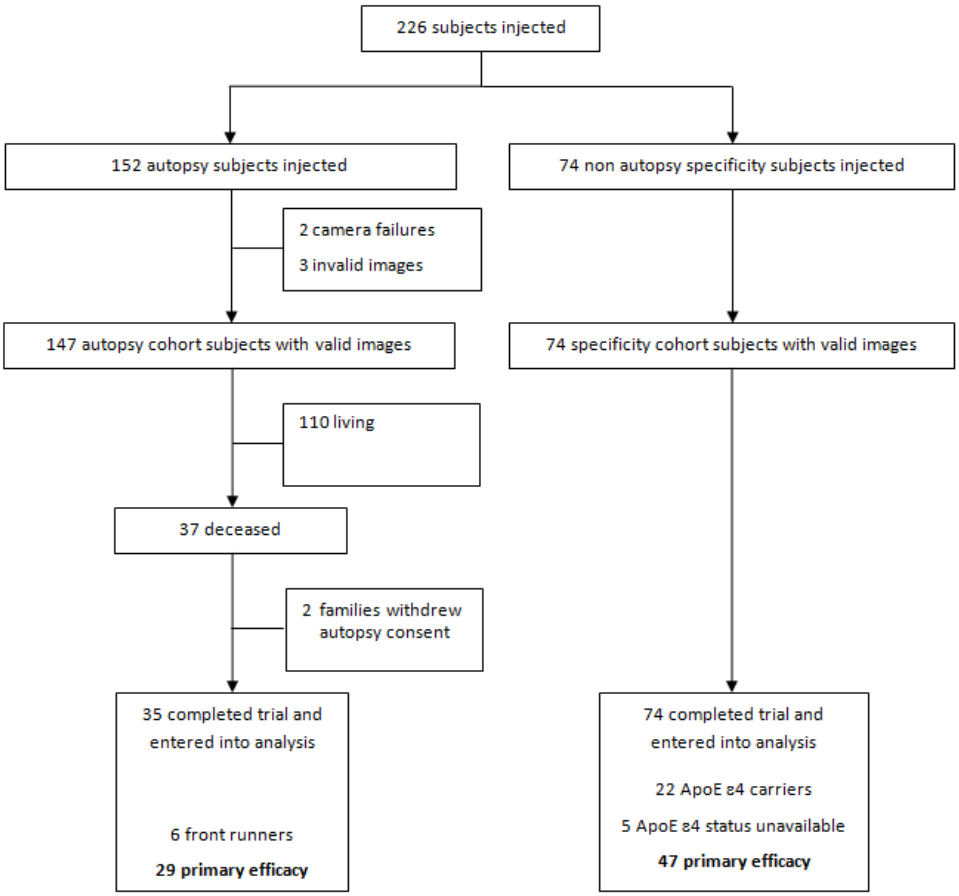
* copied from the NDA submission

Reviewer comments: There is a large difference in mean and median subject age between the autopsy and "specificity" cohorts. The majority of subjects in both cohorts were Caucasians, which reflects the general U.S. population.

6.5 Subject Disposition

The A07 trial enrolled 226 subjects: 152 in the "autopsy" cohort and 74 in the "specificity" cohort. Subject disposition in the A07 trial is summarized in Figure 1:

Figure 1: A07 Trial Subject Disposition*



* copied from the NDA submission

Of the 152 subjects in the "autopsy" cohort, 147 had valid images. At the end of the study, 37 subjects had died in the "autopsy" cohort. Of the 37 subjects in the "autopsy" cohort, 35 completed the trial and had data available for analysis. Of these 35 subjects, 29 were designated as the primary efficacy population and 6 were "front runners" (for finalizing study methods and therefore not included in the primary efficacy analysis).

Of the 74 subjects in the "specificity" cohort, 27 were excluded from the primary efficacy population because they were either ApoE ε 4 allele carriers or their ApoE ε4 genotype was not available. Thus, the 47 control subjects comprised of the primary efficacy population for the specificity analysis.

The 27 protocol deviations in the A07 trial are summarized Table 4:

Table 4: Protocol Deviations in A07 Trial: All Subjects*

	Autopsy Cohort N=152		Specificity Cohort N=74	
Description of Protocol Deviation	**n**	**Subject Number**	**n**	**Subject Number**
Physician not present pre- and post-dose	0	--	11	145-009, 145-010, 145-011, 145-012, 145-013, 145-014, 145-015, 145-016, 145-017, 145-018, 145-020
Wechsler immediate recall score was below study criterion	0	--	3	144-001, 144-009, 271-027
Wechsler immediate and delayed recall scores were below study criteria	0	--	2	321-012, 321-014
MMSE, Wechsler immediate and delayed recall scores were below study criteria	0	--	2	321-007, 321-015
PET scan started significantly more than 80 minutes post-injection	1	054-012	1	062-012
Brain removed more than 24 hours after death	1	059-003	0	--
Subject died more than 1 year after florbetapir-PET imaging	1	134-001	0	--
Subject received a radiation treatment the day before florbetapir-PET imaging	1	062-001	0	--
Subject could not tolerate the 10-minute PET scan	1	060-010	0	--
Subject had hepatitis C	1	064-001	0	--
Subject did not meet inclusion criterion, 18 to 40 years old	0	--	1	140-003
Wechsler delayed recall score was below study criterion	0	--	1	321-013

* copied from the NDA submission

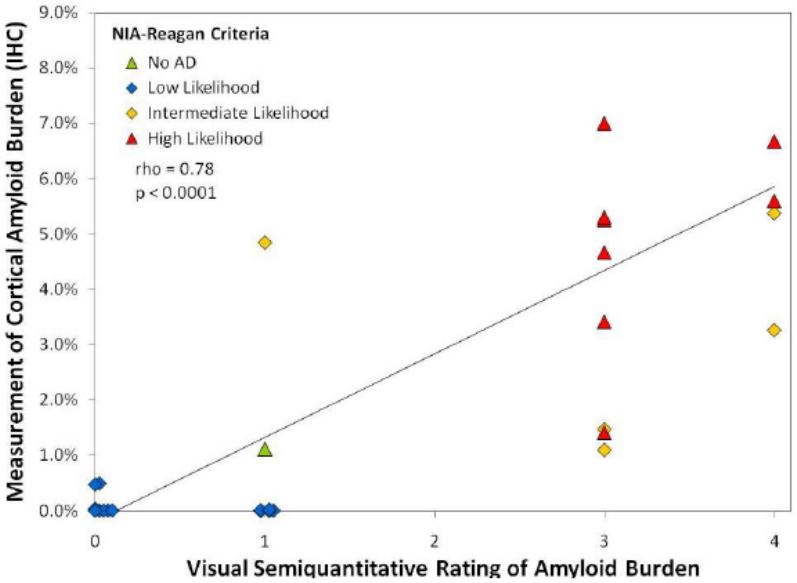
Reviewer comments: There were 27 protocol deviations in the A07 trial (~12% of total enrollees). The most common deviation was that the physician was absent before and after tracer administration (11 cases at 1 center). All deviations were considered as minor, and unlikely to have a significant impact on the trial endpoint variables assessed by the reviewer.

6.6 Analysis of Primary Endpoint(s)

6.6.1. "Autopsy" cohort

The primary endpoint is a significant correlation between the semi-quantitative visual rating of amyloid burden on the PET scan and the cortical amyloid burden at autopsy as assessed by quantitative IHC. Spearman's Correlation was used to assess the correlation. Figure 2 is the sponsor's correlation result:

Figure 2: Correlation between Semi-quantitative Visual Rating of Cortical Amyloid Burden with Immunohistochemistry (IHC)*



* copied from the NDA submission

Reviewer comments: Although the Spearman's correlation (rho) is statistically significant, the wide vertical distribution of data points for median PET ratings of 1, 3 and 4 suggests that a given PET rating will not likely predict the exact percent cortical amyloid burden. For a median PET rating of 3, the IHC % area occupied by amyloid can range from ~1% to ~7%.

Importantly, each data point in Figure 2 represents the median rating from 3 readers, which might obscure inter-reader variability. Analysis of ratings by each of the PET readers (readers 1, 2, 3) confirmed the high variability.

Table 5 summarizes the information on IHC as well as individual reader ratings and median ratings for all 35 subjects who underwent autopsy. Importantly, in 10 of 35 subjects (29%), there is at least 1 reader whose rating of global amyloid burden on PET images differed from that of the other 2 readers by at least 2 ratings on the 5-point scale (0-4).

The sponsor's submission defined post-hoc thresholds for converting the various scales to a binary scale as follows: (1) for the semi-quantitative 0-4 scale, 0, 1 was considered negative and 2, 3, or 4 as positive, (2) for quantitative IHC, $< 1\%$ was considered negative and $\geq 1\%$ as positive, (3) for the number of neuritic plaques on silver staining, ≤ 5 plaques was considered negative, and >5 plaques as positive.

Table 5: Inter-reader Variability Analysis of "Autopsy" Cohort

	Subject ID	IHC %	Pos/Neg by IHC*	Reader			
				1	2	3	Median
1	054-002	0.001	Neg	1	1	1	1
2	060-014	0.001	Neg	1	0	3	1
3	145-019	0.001	Neg	1	0	2	1
4	217-006	0.005	Neg	1	0	0	0
5	054-010	0.007	Neg	1	0	0	0
6	057-007	0.007	Neg	1	1	3	1
7	066-021	0.009	Neg	0	0	0	0
8	059-003	0.011	Neg	1	0	0	0
9	217-001	0.011	Neg	1	0	0	0
10	061-010	0.016	Neg	1	0	1	1
11	152-001	0.029	Neg	1	0	1	1
12	062-001	0.042	Neg	1	0	0	0
13	054-003	0.150	Neg	0	0	0	0
14	064-001	0.474	Neg	0	0	0	0
15	061-001	0.492	Neg	0	0	0	0
16	522-001	1.105	Pos	4	3	3	3
17	064-005	1.114	Pos	1	1	0	1
18	062-004	1.418	Pos	4	1	3	3
19	217-003	1.477	Pos	3	1	3	3
20	132-001	3.272	Pos	4	3	4	4
21	134-001	3.421	Pos	4	2	3	3
22	057-002	3.628	Pos	4	1	1	1
23	134-006	4.675	Pos	4	3	3	3
24	522-003	4.852	Pos	1	1	1	1
25	053-001	5.266	Pos	3	1	3	3
26	145-007	5.314	Pos	4	3	3	3
27	134-004	5.385	Pos	4	4	3	4
28	060-004	5.391	Pos	4	1	2	2
29	066-001	5.608	Pos	4	3	4	4
30	217-005	6.686	Pos	4	3	4	4
31	522-005	7.008	Pos	3	1	3	3
32	145-001	7.923	Pos	4	1	4	4
33	134-002	8.621	Pos	4	2	4	4
34	522-008	9.114	Pos	4	3	3	3
35	137-005	9.442	Pos	4	3	4	4

* Post-hoc threshold for IHC: >1% is positive and < 1% is negative for amyloid burden
: Incorrect median rating according to the IHC threshold.
: Rating higher or lower by at least 2 ratings compared to other two readers
: Rating higher or lower by 3 ratings compared to other two readers

Table 6 summarizes performance characteristics as determined by the sponsor:

Table 6: Analysis for Median Visual Rating with Post-hoc NIA-Reagan Threshold*

		Reference Standard: NIA-Reagan		
Florbetapir-PET Image Outcome:		Positive (Intermediate, High) (N=19)	Negative (No AD, Low) (N=16)	
Semi-quantitative Visual Blinded Read	Positive (2,3,4)	18	0	PPV = 100%
	Negative (0,1)	1	16	NPV = 94%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 97%

* copied from the NDA submission

Reviewer comments: NIA-Reagan, the reference standard, is a determination of Alzheimer's disease probability. This determination incorporates not only amyloid burden but also neurofibrillary tangle burden. The amyloid burden used to determine the NIA-Reagan Alzheimer's Disease probability is derived from counting neuritic plaques (silver staining).

The reviewer determined performance characteristics (Table 7) using the 1% IHC threshold as the SOT rather than the NIA-Reagan scale for AD probability since Amyvid is intended to detect amyloid rather than diagnose AD. In addition, the quantitation of amyloid burden by IHC was fully automated and may therefore be less subject to bias compared to silver staining for which plaques are counted by the neuropathologist.

Table 7 demonstrates the following differences: the number of subjects positive by the truth or reference standard increased from 19 to 20, sensitivity decreased from 95% to 85%, and NPV decreased from 94% to 83%. Sensitivity and specificity for each reader and the median read are summarized in Table 8. That Reader 2 demonstrates a lower sensitivity (55%) compared to the other readers is not surprising given the high inter-reader variability, as described above. Accuracy by the individual readers appears as follows: reader 1 > 3 > 2. Based on

Table 5 and Table 8, Reader 2 appears to have "undercalled", and reader 3 may have "overcalled" some PET images when IHC is the truth standard.

Table 7: Analysis for Median Visual Rating with Post-hoc IHC Threshold

		Neuropathology (IHC)		
		Positive (IHC ≥ 1%), n= 20	Negative (IHC <1%), n=15	
Visual Semi-quantitative Rating	Positive (2, 3, 4)	17	0	PPV = 100%
	Negative (0, 1)	3	15	NPV = 83%
		Sensitivity = 85%	Specificity = 100%	Accuracy = 92%

Table 8: Analysis for Agreement of Median and Individual Visual Rating

	Sensitivity (%)	Specificity (%)
Reader 1	90	100
Reader 2	55	100
Reader 3	85	80
Median	85	100

Summary of the "autopsy" cohort results: Although the primary endpoint of correlation between median PET read on a semi-quantitative 5-point scale (0-4) and amyloid burden by IHC was met, several issues--including (a) high inter-reader variability, (b) small sample size of 29, (c) undetermined clinical meaning of post-hoc thresholds, (d) wide range of true amyloid burden for some PET ratings, and (e) absence of the population of intended use in the enrolled subjects--cast doubt on the validity, reproducibility, and clinical utility of Amyvid.

6.6.2. Young, Cognitively Normal Cohort

The primary endpoint for this cohort is that the specificity of PET imaging would be ≥ 90% in young, cognitively normal subjects. This endpoint was met (Table 9).

Three readers (Readers 4, 5, 6) blind to clinical information rated Amyvid PET images of the 47 young, cognitively normal, ApoE ε4 negative subjects on a binary scale (+ or – for amyloid). The majority PET read was used to determine performance characteristics. Of note, the negative amyloid status of these subjects was presumed rather than confirmed by histopathology. To minimize bias, the sponsor added PET images from the first 40 subjects in the autopsy cohort whose PET images had a median read of 2, 3, or 4 (suggesting amyloid positivity).

Table 9: Sensitivity and Specificity of Visual Assessment in the Young, Cognitively Normal Subjects*

		Reference Standard: Presumed Amyloid Status		
Florbetapir-PET Image Outcome:		Positive (Autopsy Cohort[a]) (N=40)	Negative (Young, Healthy Controls[b]) (N=47)	
Qualitative Visual Blinded Read	Positive (Aβ+)	38	0	PPV = 100%
	Negative (Aβ-)	2	47	NPV = 96%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 98%

* copied from the NDA submission

Reviewer comments: A significant limitation of this endpoint is that the young, cognitively normal subjects do not truly represent a "specificity" cohort since they are not in the population of intended use. The true specificity cohort would comprise of subjects presenting with memory impairment or cognitive decline who are confirmed to be negative for amyloid. Furthermore, although there is high specificity in the cohort, the absence of amyloid in these young subjects is presumed rather than confirmed by pathology. The reviewer will focus on the "specificity" cohort data analysis since the PET image readers for this cohort applied the binary interpretation method, and this is the sponsor's proposed method for routine clinical use if Amyvid is approved. A total of 74 were enrolled in the cohort, but only 47 subjects were confirmed as negative carriers of ApoE ε4 (genetic risk factor for AD). Thus, data from only these 47 subjects were used in the primary endpoint analysis for this cohort. Specificity results for each reader are summarized in Table 10.

Table 10: By-reader Specificity for the 47 Young, Cognitively Normal Subjects

	Read Negative / Presumed Negative	%
Reader 4	47 / 47	100
Reader 5	46 / 47	98
Reader 6	47 / 47	100
Majority	47 / 47	100
All Reads	140 / 141	99

The sponsor added PET images from 40 subjects in the "autopsy" cohort into the "specificity" cohort image pool to minimize bias. The images from these 40 subjects had a median PET read by Readers 1, 2, and 3 suggestive of amyloid presence (median rating of 2, 3, or 4 on a 5-point scale). Of these 40 PET images, 38 (95%) were also read as positive for amyloid by the majority of Readers 4, 5, and 6 (Table 11, Table 12). Only 14 of these 40 subjects underwent autopsy and had pathology results. PET images of all 14 subjects were interpreted as positive by majority read; only 2 of these PET images were read as negative, each by a single reader so the majority read was not affected (Table 11, Table 13).

Ideally, PET images from all 35 subjects in the "autopsy" cohort would have been randomized into the image pool of the "specificity" cohort for assessment of performance characteristics using the binary scale for PET images and pathology as the standard of truth. An additional concern is that structural information on CT images (when available) could have biased readers regarding amyloid presence or absence: the young, cognitively normal subjects (mean age of 26) would likely show less cortical atrophy than the "autopsy" cohort subjects (mean age of 80).

Table 11: Summary of 40 "Autopsy" Subjects (PET Images Randomized in with Those from Young, Cognitively Normal Subjects)

	Subject	Neuritic Plaque (CERAD)*	Reader			
			4	5	6	Majority
1	522-001	More than sparse	Pos	Pos	Pos	Pos
2	062-004		Pos	Pos	Pos	Pos
3	217-003		Pos	Pos	Neg	Pos
4	134-001		Pos	Pos	Pos	Pos
5	134-006		Pos	Neg	Pos	Pos
6	053-001		Pos	Pos	Pos	Pos
7	145-007		Pos	Pos	Pos	Pos
8	060-004		Pos	Pos	Pos	Pos
9	066-001		Pos	Pos	Pos	Pos
10	217-005		Pos	Pos	Pos	Pos
11	145-001		Pos	Pos	Pos	Pos
12	134-002		Pos	Pos	Pos	Pos
13	522-008		Pos	Pos	Pos	Pos
14	137-005		Pos	Pos	Pos	Pos
15	057-001	NA	Neg	Neg	Neg	Neg
16	057-005		Pos	Pos	Pos	Pos
17	059-001		Pos	Pos	Pos	Pos
18	059-005		Pos	Pos	Pos	Pos
19	059-006		Pos	Pos	Pos	Pos
20	059-012		Pos	Neg	Pos	Pos
21	060-001		Pos	Pos	Pos	Pos
22	060-003		Pos	Pos	Pos	Pos
23	060-005		Pos	Neg	Pos	Pos
24	060-006		Pos	Pos	Pos	Pos
25	062-002		Pos	Pos	Pos	Pos
26	062-003		Pos	Pos	Pos	Pos
27	062-005		Pos	Pos	Pos	Pos
28	064-002		Pos	Pos	Pos	Pos
29	129-001		Pos	Pos	Pos	Pos
30	129-004		Neg	Neg	Neg	Neg
31	134-005		Pos	Pos	Pos	Pos
32	137-001		Pos	Pos	Pos	Pos
33	145-002		Pos	Pos	Pos	Pos
34	145-003		Pos	Pos	Pos	Pos
35	145-004		Pos	Pos	Pos	Pos
36	145-005		Pos	Pos	Pos	Pos
37	145-006		Pos	Neg	Pos	Pos
38	522-002		Pos	Pos	Pos	Pos
39	522-004		Pos	Pos	Pos	Pos
40	522-007		Pos	Pos	Pos	Pos

* only 14 of the 40 subjects underwent autopsy, and all were "more than sparse" for neuritic plaques (≥ 6 neuritic plaques in the microscopic field)

Table 12 summarizes the by-reader "sensitivity" for the 40 subjects from the "autopsy" cohort whose images were randomized into the image pool from the young, cognitively normal subjects. "Sensitivity" is in quotes here because the reference standard was the median read by a different set of readers rather than pathology. Only 14 of these 40 subjects had histopathology results as the standard of truth (Table 13).

Table 12: By-reader "Sensitivity" for the Presumed Positive Group (PET Images Randomized in with Those from Young, Cognitively Normal Subjects), n=40

	Read Positive per Positive by "Autopsy" Cohort Readers*	%
Reader 4	38 / 40	95
Reader 5	34 / 40	85
Reader 6	37 / 40	93
Majority	38 / 40	95
All Reads	109 / 120	91

* Fourteen of 40 subjects had histopathology result, all 14 with "more than sparse" neuritic plaques

Table 13: By-reader Sensitivity for the Pathology Confirmed Positive Group (PET Images Randomized in with Those from Young, Cognitively Normal Subjects), n=14

	Read Positive per Silver Staining "More Than Sparse" for Neuritic Plaques	%
Reader 4	14 / 14	100
Reader 5	13 / 14	93
Reader 6	13 / 14	93
Majority	14 / 14	100
All Reads	40 / 42	95

* All 14 had histopathology result of "more than sparse" neuritic plaques

Readers 4, 5, and 6 read PET images for 114 subjects: 74 subjects were young and cognitively normal, the other subjects were the first 40 from the "autopsy" cohort with amyloid-positive images according to Readers 1, 2, and 3 (median read $\geq$ 2). The inter-reader agreement among the 3 readers for these 114 images is over 90% (Table 14):

Table 14: Inter-reader Agreement for Visual Qualitative Binary Rating of PET Images from 74 Young, Cognitively Normal and 40 "Autopsy" Cohort Subjects*

	n	Observed Agreement (%)	Kappa Statistic	95% CI
Reader 4 vs. Reader 5	114	94	0.86	0.76 - 0.96
Reader 4 vs. Reader 6	114	99	0.98	0.94 - 1.00
Reader 5 vs. Reader 6	114	93	0.84	0.73 - 0.95

* copied from the NDA submission

Summary of the "specificity" cohort results: Although the primary endpoint of >90% specificity in the 47 young, cognitively normal subjects was met, the amyloid negative status (SOT) was presumed rather than confirmed by pathology. Although the majority read was positive for all "autopsy" cohort subjects randomized into the image pool, there were only 14 subjects whose amyloid positive status was confirmed by the pathology. Ideally, PET images of all 35 subjects who underwent autopsy would have been randomized into the image pool of the "specificity" cohort so that performance characteristics of the sponsor's proposed reading method for routine clinical use of Amyvid PET images could be assessed relative to amyloid status by pathology.

6.7 Analysis of Secondary Endpoints(s)

The secondary endpoint of the A07 trial is regional correlation between visual rating (0-4 scale) of the PET images and cerebral amyloid burden by immunohistochemistry (IHC) (Table 15). These results were verified by the reviewer.

Table 15: Regional Correlation Between Semi-quantitative Visual Ratings (0-4) of Cerebral Amyloid Burden with Immunohistochemistry (IHC), n=35

	Avid Analysis		Reviewer Analysis	
	Spearman's rho	95% CI	Spearman's rho	95% CI
Frontal	0.69	0.44, 0.84	0.71	0.48, 0.84
Temporal	0.68	0.42, 0.84	0.68	0.44, 0.82
Precuneus	0.75	0.53, 0.88	0.76	0.56, 0.87
Parietal	0.77	0.56, 0.88	0.72	0.50, 0.84
Ant Cingulate	0.74	0.51, 0.87	0.75	0.54, 0.84
Post Cingulate	0.70	0.44, 0.85	0.68	0.43, 0.82

* 95% CI: 95% confidence interval

6.8 Other Endpoints

1. In the exploratory endpoint analysis, the sponsor claimed that "there is correlation between quantitative SUVR (standard uptake value ratio) and cortical amyloid IHC result (rho=0.75) and SUVR analysis (using the post-hoc 1.10 positive cutoff) showed 100% agreement with autopsy results".

Reviewer comment: SUVR is a multifactorial equation generated from SUV. SUV (standard uptake value) indicates the radioactive signal of the PET tracer in the specific area. SUV is a quantitative parameter in the PET functional imaging assessment and widely used in the FDG PET imaging interpretation. But SUV can be affected by many factors, including image noise, low image resolution, and user biased region of interest (ROI) selection [14]. SUVR can be affected by more factors than SUV. According to the protocol, there were multiple steps for the SUVR calculation "*the SUVR in the submission is the ratio of cortical to cerebellar signal, which were calculated for the following 6 target cortical brain regions: frontal, temporal, precuneus, parietal cortex, anterior cingulate, and posterior cingulate using whole cerebellum as the reference region. The main SUVR efficacy endpoint for quantitative evaluation of each subject was the mean of the SUVRs for the 6 cortical target regions."* Obviously, each step of the measurements described above can influence the SUVR value. The reviewer considers a ratio as a fraction, here the cerebral SUV as numerator and the cerebellar SUV as denominator. Application of the ratio here is based on the assumption that (a) the cerebellar SUV (denominator) is relatively stable and not closely correlated with cerebral SUV (numerator), and (b) there is good correlation between the cerebral SUV and SUVR--that is, SUVR increases with the increase of cerebral SUV and vice versa. However, detailed data analysis shows that these assumptions are violated: the data demonstrate that there is good correlation between cortical SUV and cerebellar SUV with a Pearson's correlation of 0.92 ($p < 0.0001$) and an unimpressive correlation between the cortical SUV and SUVR with Pearson's correlation of only 0.5 (though still statistically significant with $p = 0.003$). Pearson's analysis rather than Spearman analysis is used here since both SUV and SUVR are continuous variables. According to the sponsor, the total sample size for the analysis is 33, and two SUV data sets are missing. The SUVR cutoff of 1.1 is a post-hoc threshold which might be misleading. Analysis of the available data demonstrates that the range of SUVR is quite narrow [from 0.81 (minimal) to 1.91 (maximal) (n

= 35)] whereas the range of IHC is quite broad, [from 0.001 to 9.44 (Table 16)], suggesting that SUVR values did not reflect the histopathology results quantitatively.

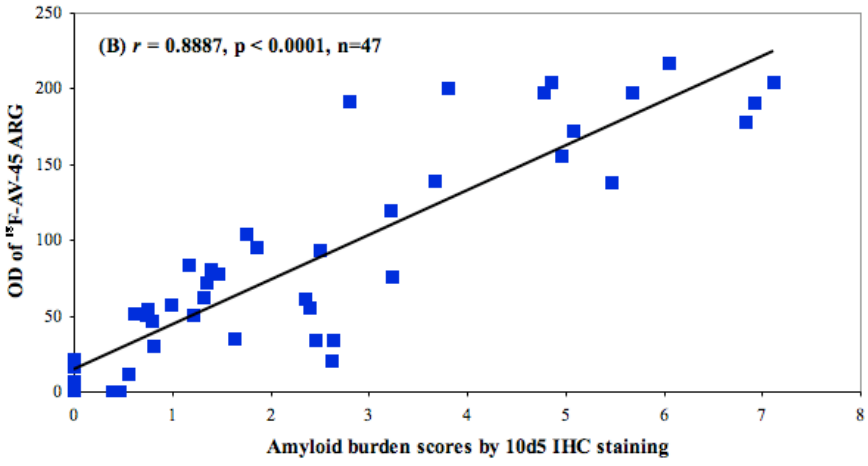
Table 16: Statistics of Pathology (IHC and Silver Stain) and Quantitative Imaging Parameters (SUV and SUVR) in "Autopsy" Cohort

Variable	n	Mean	SD	Median	Minimum	Maximum
Cerebral IHC	35	2.914	3.161	1.418	0.001	9.442
SUVR	35	1.207	0.284	1.196	0.807	1.911
Cerebral SUV	33	0.964	0.699	0.788	0.037	3.735
Cerebellar SUV	33	0.774	0.484	0.736	0.038	2.294

Overall, there is no solid evidence available to demonstrate that SUVR is a reliable quantitative parameter for PET imaging assessment.

2. The strong *in vitro* correlation using radiolabeled Amyvid does not translate into high *in vivo* correlation using Amyvid. The sponsor claimed that the preclinical studies showed that the drug selectively binds to and labels amyloid in human brain tissue and that binding intensity of the drug is quantitatively correlated with the density of amyloid quantified by IHC (Figure 3).

Figure 3: Correlation between Amyvid Autoradiography Signal Intensity (Optical Density, OD) with Amyloid Aggregate Deposition Measured by Immunohistochemistry (IHC)*



* copied from the NDA submission

Reviewer comments: Although the *in vitro* correlation may be impressive, the *in vivo* correlation between cortical global or regional PET imaging signal (SUV) and amyloid burden measured by IHC (Table 17) is not as high.

Table 17: Correlation between Global and Regional Signal (SUV) and Amyloid Burden (IHC), n=33

	Pearson's r
Cerebral Global	0.50
Frontal	0.49
Temporal	0.45
Precuneus	0.48
Parietal	0.45
Ant Cingulate	0.51
Post Cingulate	0.49

3. Not all PET images in the A07 trial were acquired with CT. Nowadays, PET/CT fusion is almost routine for functional imaging acquisition and interpretation. CT imaging allows functional imaging obtained by PET, which depicts the spatial distribution of metabolic or biochemical activity in the body, to be more precisely aligned or correlated with anatomic imaging. According to the submission, 40 of the 221 PET images in the A07 trial were acquired without CT. This raises the possibility that inconsistent CT acquisition may have introduced variability into the results.

6.9 Subpopulations

Because Amyvid is intravenously administered, fully bio-available, and very rapidly cleared from plasma, pharmacokinetic studies in special populations were not performed. However, population analysis of PET scan data revealed no difference in drug binding and blood clearance kinetics in probable AD patients or cognitively healthy controls. No significant differences were seen among individuals of different gender, race and age.

6.10 Analysis of Clinical Information Relevant to Dosing Recommendations

Study A03 evaluated the range of effective doses for Amyvid. Twenty subjects (9 AD, 11 healthy controls) were enrolled in the study. Nine subjects and 11 subjects were assigned to the

111-MBq (3 mCi) and 370-MBq (10 mCi) dose groups, respectively. Images were evaluated qualitatively to determine acceptable image quality between 3 and 10 mCi dose levels. A blinded reader rated the quality of each image on a 5-point scale (where a score of 5=excellent and 1=poor). Visual assessments of image quality were better for the 370-MBq dose than the 111-MBq dose group although there was no significant difference. Based on the improvement in the visual image quality ratings, a dose of 370-MBq was recommended as the reference dose for clinical application and for all subsequent clinical trials.

6.11 Discussion of Persistence of Efficacy and/or Tolerance Effects

A03 study also evaluated the optimal time window (time from the tracer injection to proposed imaging in clinical use) of Amyvid. The result showed very stable brain radioactive signal between 30 and 90 minutes after injection and imaging acquisition 30-50 minutes post drug injection was decided accordingly.

6.12 Additional Efficacy Issues/Analyses

A04 study evaluated the test-retest reproducibility of Amyvid PET imaging. Twenty subjects (10 clinically diagnosed AD and 10 healthy controls) were imaged twice on 2 separate days with 1 month. The images were read by a single reader with binary qualitative (amyloid positive or negative) reading and the result is summarized in Table 18:

Table 18: Agreement for Binary Assessment between Test and Retest Images

	n	Agreement (%)	Kappa (95% CI)
Probable AD	10	90	0.74 (0.26, 1.00)
Healthy Control	10	100	1.00 (1.00, 1.00)

7 Review of Safety

Safety Summary

Safety data for Amyvid from all 7 clinical studies (n=496 subjects) reveal no important safety signals for Amyvid administration. There have been no deaths or serious adverse events (SE) attributable to the drug as determined by the study investigators. The safety data from clinical

laboratory evaluations, vital sign monitoring, and ECG assessments have produced no important concerns regarding Amyvid use.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from the 496 subjects who received at least one dose of Amyvid in clinical trials is summarized in Table 19:

Table 19: The Studies in the Integrated Safety Analysis

Phase	Study ID	Subjects # (n)	Dosing (IV administration)
1	A01	32	10 mCi, single
	A02	9	10 mCi, single
	A03	20	3 mCi and 10 mCi single
	A04	25	10 mCi 2 doses within 4 weeks
2	A05	184	10 mCi, single
3	A07	226	10 mCi, single
		Total 496	

7.1.2 Categorization of Adverse Events

Treatment-emergent adverse event (TEAE) is an undesirable experience, sign, or symptom that started, or worsened, in intensity or frequency at the time of or 48 hours after the administration of Amyvid.

An SAE can result in any of the following outcomes including death, life-threatening, inpatient hospitalization, persistent or significant disability, congenital anomaly or birth defect, or other important medical events.

The assessment of the relationship of an AE to the administration of the drug (remote, possible, and probable) was made using all available information. The intensity/severity of an AE is classified as mild, moderate and severe.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Amyvid safety data were pooled across the 7 clinical studies with a total of 496 subjects summarized Table 19 (section 7.1.1 above).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All 496 patients exposed were adults > 18 years of age who received at least one administration of Amyvid ranging from 3 mCi to 10 mCi (the proposed dosage). Twenty five subjects in A04 test-retest trial received two doses of the drug within one month, summarized in Table 18 (section 6.1.10 above). There is no specific sample size required for radiopharmaceutical safety assessment according to FDA guidelines. The data from 496 subjects appear adequate.

7.2.2 Explorations for Dose Response

The phase 1 A03 study compared the 3 mCi and 10 mCi doses of Amyvid administered with regards to dose escalation estimates. The final, proposed dose of 10 mCi was determined based upon adequate imaging results and acceptable radiation dosimetry estimates obtained in the phase 1 studies.

7.2.3 Special Animal and/or In Vitro Testing

The pre-clinical safety pharmacology studies did not reveal risk of adverse effects of the drug on the CNS or the cardiovascular system, with the NOAEL at least 100-fold higher than the maximum intended dose from a single dose of the drug to humans.

7.2.4 Routine Clinical Testing

The routine clinical testing of study subjects was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

[Please see Clinical Pharmacology section (4.4.2) for further details]

There have been no human studies to investigate Amyvid drug interactions. Drug interactions with Amyvid are considered unlikely based on the nature and action mechanism of the drug.

Amyvid use in patients with impaired excretory or metabolic function has not been evaluated because of its single dose, microgram dosing regimen. The effects of age and gender differences on the drug pharmacokinetics have not been evaluated.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Amyvid is a new molecular entity and pharmacological effects from the drug are not observed in humans following the intravenous administration of the proposed dose of ≤ 50 μg. The non-radioactive ingredient of the drug is an analog of PiB, which is a fluorescent analog of thioflavin T. There are multiple PiB and PiB analog PET radio-tracers with radioisotope of F-18, C-11, and I-123 [for Single photon emission computed tomography (SPECT)] in clinical trials under IND. The first human study with PiB-C-11 was in 2004 [9]. There have been thousands of human subjects who have been administered the PiB PET tracer, and safety data of the drug appears benign.

7.3 Major Safety Results

7.3.1 Deaths

There were a total of two death reports with administration of Amyvid. The cause of death of both cases was considered un-related to Amyvid. The first case was a 78-year-old hospice dwelling male with Parkinson's disease and dementia in A07 who experienced a severe AE and died from respiratory failure around 29 hours post-dosing, during the 48-hour safety monitoring period. The relationship of the death to the drug was considered remote (unlikely) by the investigator at the site. The second death case was outside of the Avid-sponsored clinical studies. An 83-year-old male AD patient with multiple medical issues was in a therapy trial in which Amyvid was used as an imaging biomarker for therapeutic effect. The subject experienced a fatal hemorrhagic stroke one day after dosing and died two days later. The causal relationship of death to the drug was deemed unlikely by the site investigator.

7.3.2 Nonfatal Serious Adverse Events

There were two non-fatal SAEs and both were considered unrelated to Amyvid administration. One was an upper limb fracture 4 days post dosing. Another one outside of the Avid trial suffered an acute stroke 2 days after dosing.

7.3.3 Dropouts and/or Discontinuations

No subject withdrew from the Amyvid studies due to a TEAE.

7.3.4 Significant Adverse Events

For the safety population, the overall rate of AEs was low, with 47 of 496 (9.5%) subjects experiencing a total of 63 TEAEs (Table 20). The majority of these AEs were assessed to be mild and not related to the study drug. The most frequently reported adverse events (in descending order of frequency) were headache (9 of 496 [1.8%] subjects), musculoskeletal pain (4 of 496 [0.8%] subjects), fatigue (3 of 496 [0.6%] subjects), and nausea (3 of 496 [0.6%] subjects). Cognitively impaired subjects showed no evidence for having an increased rate of AEs.

Table 20: TEAE in Descending Order of Frequency – Safety Population*

MedDRA Preferred Term (PT)	No. (%)[a] Cognitively Impaired (N = 247)	Cognitively Normal (N = 249)	Overall (N = 496)
Number of Subjects With at Least One Adverse Event	**18 (7.3)**	**29 (11.6)**	**47 (9.5)**
Headache	5 (2.0)	3 (1.2)	8 (1.6)
Musculoskeletal pain	1 (0.4)	3 (1.2)	4 (0.8)
Fatigue	1 (0.4)	2 (0.8)	3 (0.6)
Nausea	0	3 (1.2)	3 (0.6)
Anxiety	0	2 (0.8)	2 (0.4)
Back pain	1 (0.4)	1 (0.4)	2 (0.4)
Claustrophobia	0	2 (0.8)	2 (0.4)
Hypertension	1 (0.4)	1 (0.4)	2 (0.4)
Insomnia	1 (0.4)	1 (0.4)	2 (0.4)
Neck pain	2 (0.8)	0	2 (0.4)
Abdominal distension	1 (0.4)	0	1 (0.2)
Blood pressure increased	1 (0.4)	0	1 (0.2)
Chest pain	0	1 (0.4)	1 (0.2)
Chills	1 (0.4)	0	1 (0.2)
Constipation	1 (0.4)	0	1 (0.2)
Diarrhoea	0	1 (0.4)	1 (0.2)
Dizziness	0	1 (0.4)	1 (0.2)
Dysgeusia[b]	0	1 (0.4)	1 (0.2)
Feeling cold	0	1 (0.4)	1 (0.2)
Flatulence	0	1 (0.4)	1 (0.2)
Flushing	0	1 (0.4)	1 (0.2)
Haematuria	0	1 (0.4)	1 (0.2)
Infusion site extravasation	1 (0.4)	0	1 (0.2)
Infusion site rash	0	1 (0.4)	1 (0.2)
Injection site haemorrhage	0	1 (0.4)	1 (0.2)
Injection site irritation	0	1 (0.4)	1 (0.2)
Musculoskeletal stiffness	1 (0.4)	0	1 (0.2)
Oedema peripheral	1 (0.4)	0	1 (0.2)
Pain	0	1 (0.4)	1 (0.2)
Palpitations	0	1 (0.4)	1 (0.2)
Parosmia	0	1 (0.4)	1 (0.2)
Pruritus generalized	0	1 (0.4)	1 (0.2)
Respiratory failure	1 (0.4)	0	1 (0.2)
Sinus headache	0	1 (0.4)	1 (0.2)
Supraventricular extrasystoles	1 (0.4)	0	1 (0.2)
Upper limb fracture	1 (0.4)	0	1 (0.2)
Urine color abnormal	1 (0.4)	0	1 (0.2)
Urticaria	0	1 (0.4)	1 (0.2)
Ventricular extrasystoles	1 (0.4)	0	1 (0.2)
Vessel puncture site haematoma	0	1 (0.4)	1 (0.2)
Vomiting	0	1 (0.4)	1 (0.2)
White blood cell count increased	0	1 (0.4)	1 (0.2)

* copied from the NDA submission

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent adverse events (TEAE) are those AEs experienced anytime following administration of Amyvid. In the safety population, 47 of 496 (9.5%) subjects experienced a total of 63 TEAEs with the top five being headache, musculoskeletal pain, fatigue, nausea and anxiety (Table 20, in section of 7.3.4 above).

7.4.2 Laboratory Findings

There were no clinically meaningful predose to postdose changes in the mean values associated with any laboratory value. While some predose to postdose changes reached statistical significance ($P < 0.05$), many moved in a non-detrimental direction (e.g., decrease in liver enzymes). Most of the potentially clinically significant (PCS) laboratory values in individual subjects were also PCS at the predose or screening laboratory values. In addition, only 1 of 496 subjects in the Safety Population had clinical laboratory value that was considered an AE by the principal investigator (increase of white blood cell count (WBC) from 9.9 predose to 11.2 postdose).

7.4.3 Vital Signs

The vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, respiratory rate, and body temperature, were measured at baseline, 0, 75, and > 110 minutes postdose. Statistically significant increases in blood pressure were seen between screening and baseline measurements (i.e., prior to administration of drug) as well between baseline and both t = 0 and t = 75 minutes post dose. The changes in individual subjects occasionally met criteria for potential clinical significance, particularly at the 75-minute postdose measurement (Table 21). However, since this was the time point when the patient was getting off of the table from the PET procedure, changes at this time point could be procedural. In general, the subjects that had changes that met criteria for potential clinical significance had evidence for more general blood pressure variability with significant increases in blood pressure levels prior to study drug administration (i.e. the predose blood pressure was increased as compared to screening). The

changes in blood pressure after drug administration were generally not thought to be clinically significant by the site investigators and all resolved without treatment.

Table 21: SBP and DBP Change from Baseline to Postdose (in Minutes)*

Paramter Postdose Time Point (min)	Statistic	Modified Safety Population, No. (%)			No. (%)
		Cognitively Impaired (N = 145)	Cognitively Normal (N = 199)	Overall (N = 344)	A07 AC Subjects (N = 152)
Systolic blood pressure, mmHg					
0	N	145	115	260	—
	Mean (SD)	2.2 (9.03)	3.1 (10.43)	2.6 (9.67)	—
	95% CI	0.74, 3.70	1.13, 4.98	1.41, 3.77	—
	Median	2.0	2.0	2.0	—
	Min, Max	–27, 34	–24, 58	–27, 58	—
	P value	0.0036	0.0021	< 0.0001	—
75	N	140	185	325	151
	Mean (SD)	4.6 (12.85)	0.8 (11.31)	2.4 (12.13)	3.8 (15.17)
	95% CI	2.43, 6.73	–0.86, 2.42	1.09, 3.74	—
	Median	4.0	0.0	2.0	2.0
	Min, Max	–47, 66	–30, 44	–47, 66	–41, 47
	P value	< 0.0001	0.3521	0.0004	0.0023
> 110	N	24	39	63	—
	Mean (SD)	–2.4 (13.78)	4.7 (13.77)	2.0 (14.09)	—
	95% CI	–8.19, 3.44	0.23, 9.15	–1.55, 5.55	—
	Median	–1.5	7.0	3.0	—
	Min, Max	–28, 26	–30, 46	–30, 46	—
	P value	0.4071	0.0398	0.2642	—
Diastolic blood pressure, mmHg					
0	N	145	115	260	—
	Mean (SD)	1.8 (5.94)	0.6 (5.55)	1.3 (5.79)	—
	95% CI	0.81, 2.76	–0.41, 1.64	0.56, 1.97	—
	Median	2.0	0.0	1.0	—
	Min, Max	–23, 19	–25, 18	–25, 19	—
	P value	0.0004	0.2388	0.0005	—
75	N	140	185	325	151
	Mean (SD)	3.2 (7.25)	1.0 (6.74)	2.0 (7.04)	3.4 (10.44)
	95% CI	2.00, 4.43	0.07, 2.02	1.21, 2.75	—
	Median	3.0	0.0	2.0	2.0
	Min, Max	–21, 26	–28, 21	–28, 26	–26, 40
	P value	< 0.0001	0.0367	< 0.0001	< 0.0001
> 110	N	24	39	63	—
	Mean (SD)	1.7 (9.27)	0.9 (7.69)	1.2 (8.27)	—
	95% CI	–2.21, 5.62	–1.57, 3.42	–0.86, 3.30	—
	Median	0.0	1.0	1.0	—
	Min, Max	–17, 28	–21, 16	–21, 28	—
	P value	0.3761	0.4583	0.2450	—

* copied from the NDA submission

7.4.4 Electrocardiograms (ECGs)

The ECG was tested from baseline to 0, 75, and > 110 minutes postdose (Table 22). In the 344 subjects with pre and post treatment ECG results, there was a statistically significant finding with

a small (3 msec) mean increase in QTcF at the 75 minute post dose time point (shortly after completion of imaging). This change in mean QTcF may be a consequence of the algorithm used to correct for heart rate decrease rather than a true physiologic change, as the algorithm tends to under-correct when heart rate is low and produce spurious high QTc values. This is supported by the observation that the mean QTcB did not change significantly from Baseline at any postdose time point. No individuals had increases in QTcF or QTcB more than 60 msec from baseline, and no absolute QTc values exceeded 500 msec. The results suggest the drug has no significant effect on cardiac electrophysiology.

Table 22: ECG Results: Changes from Baseline to Postdose (in Minutes)*

ECG Measurement Postdose Time Point	Statistic	Modified Safety Population, No. (%)		
		Cognitively Impaired (N = 145)	Cognitively Normal (N = 199)	Overall (N = 344)
QTcF for Fridericia's Correction Formula, msec				
0 min	N	142	112	254
	Mean (SD)	0.2 (8.91)	0.7 (7.56)	0.4 (8.33)
	95% CI	–1.24, 1.72	–0.75, 2.08	–0.60, 1.46
	Median	0.0	0.0	0.0
	Min, Max	–46, 21	–16, 23	–46, 23
	P value	0.7493	0.3528	0.4138
75 min	N	139	110	249
	Mean (SD)	2.7 (10.95)	3.5 (14.76)	3.0 (12.75)
	95% CI	0.83, 4.50	0.70, 6.27	1.44, 4.62
	Median	2.0	4.0	3.0
	Min, Max	–28, 42	–106, 28	–106, 42
	P value	0.0048	0.0148	0.0002
> 110 min	N	25	33	58
	Mean (SD)	–1.1 (9.93)	0.9 (10.21)	0.1 (10.05)
	95% CI	–5.16, 3.03	–2.72, 4.52	–2.59, 2.69
	Median	1.0	0.5	0.6
	Min, Max	–28, 15	–32, 24	–32, 24
	P value	0.5961	0.6166	0.9689

* copied from the NDA submission

Reviewer comments: The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the cardiac electrical cycle. The QT interval generally represents electrical depolarization and repolarization of the left and right ventricles. The standard clinical values QTc (corrected QT), either QTcB calculated with Bazett's correction formula or QTcF with Fridericia's formula. According to the FDA guideline, the normal QTc is defined as equal to or less than ≤ 400 msec (0. 40 sec), abnormal if > 450 msec and the thresholds for trial discontinuation increases in QT/QTc to > 500 msec or of > 60 msec over baseline [15]. The

small increase of an average of 3 msec of QTcF appears to not have a significant impact on cardiac electrophysiology.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

None

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

One phase 1 study (A03) compares the 3 mCi and 10 mCi doses with a small sample size of 20 subjects. Analysis of safety data from the study indicated no significant difference between the subjects receiving the two different doses.

7.5.2 Time Dependency for Adverse Events

According to the submission, the time of onset, duration, action taken, and outcome of AEs were 48 hours post-injection of the drug. See further details in section 7.5.3 below.

7.5.3 Drug-Demographic Interactions

The incidence of AEs with Amyvid was analyzed in the subgroups including gender, race and age. TEAEs for the safety population (n=496) are analyzed separately for geriatric (≥ 65 years old) (n=307) and non-geriatric (< 65 years old) (n=189) subpopulations. There is no consistent difference in the pattern of adverse events between males and females. There is no evidence of any tolerability or special AE concerns that are specific to the geriatric subpopulation. There was no clinically significant interaction of age with lab parameters following drug administration. The only change from baseline in vital signs by age category is increase of blood pressure (see section 7.4.3). ECG with age data showed that the small but statistically significant increase in QTcF that was seen in the whole population at 75-minute postdose was similar in magnitude in both the geriatric and non-geriatric subpopulations. Overall, there were no

significant differences between race, with the incidence of adverse events in whites (9.2%) being similar to those in nonwhites (11.1%). No adverse event occurred in more than one nonwhite subject.

7.5.4 Drug-Disease Interactions

No trial data for Amyvid to Alzheimer's disease interaction is available.

7.5.5 Drug-Drug Interactions

There are no known drug interactions. Patients on or off AD medications tolerated the drug similarly well. Given the very low mass of florbetapir received in a single Amyvid administration and the very rapid clearance of the drug from circulation, alterations in the pharmacodynamics and pharmacokinetics of other commonly prescribed medications are not anticipated.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity study was conducted for Amyvid. The sponsor requested a waiver for carcinogenicity studies and the waiver was granted.

7.6.2 Human Reproduction and Pregnancy Data

There are no data on Amyvid exposure in pregnant or lactating women, including inadvertent exposure during the drug development program. It is not known if Amyvid is excreted in human milk. The sponsor requested a waiver for human reproduction and pregnancy, and the waiver was granted.

7.6.3 Pediatrics and Assessment of Effects on Growth

There are no data on Amyvid use in pediatric subjects. The sponsor requested a waiver for the assessment of safety and effectiveness of the drug in pediatric patients. The waiver was granted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

1. Overdose: since the drug is given in a controlled situation as a single-dose bolus, it is not expected to have overdose potential.
2. Drug Abuse Potential: since the drug is given in a controlled situation as a single-dose bolus, it is not expected to have potential for drug abuse.
3. Withdrawal and Rebound: since the drug is given in a controlled situation as a single-dose bolus, it is not expected to have potential for withdrawal or rebound effects.

7.7 Additional Submissions

None

8 Postmarket Experience

Since the drug has not been marketed anywhere, there is no postmarketing data available.

9 Appendices

9.1 Literature Review/References

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12. CFR 21 part 361.1 Radioactive drug for certain research uses 2009 http://law.justia.com/us/cfr/title21/21-5.0.1.1.29.html

13. Review Classification Policy: Priority (P) and Standard (S), MAPP 6020.3, CDER, FDA. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf

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15. FDA Guidance for Industry Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs 2005 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf

9.2 Labeling Recommendations

Concerns regarding the proposed label include the following:

1. There is a significant attempt to link and associate the diagnosis of AD with Amyvid in the label, which might mislead clinicians and patients. All the promotional verbal descriptions, tables and graphs in the label should be eliminated.
2. More detailed reader training information should be incorporated in the label to help the clinician use the drug.

The review will compare other approved PLR labels in the same class for consistency when the drug is considered as approvable.

9.3 Advisory Committee Meeting

A Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to discuss the issues of clinical utility, validity and reproducibility of the Amyvid PET scan is scheduled on January 20, 2011.